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Health Technology Clinical Committee Public Meeting
November 21, 2014

Craig Blackmore: Good morning, everyone. We are a little past 8:00, and we have a quorum, so I'm going to call the meeting to order. This is the November Washington State Health Technology Clinical Committee. I am Craig Blackmore. I am the Chair, and I would like to welcome the members and members of the public who might be joining us. First item of business on the agenda is Health Technology Assessment Program Update.

Josh Morse: Good morning, I am Josh Morse. I am the Program Director for the Health Technology Assessment Program, and I will go through a quick overview of the program and briefly today's topic. So, today's topic is screening and monitoring tests for osteopenia/osteoporosis. Next month's meeting is January 16th, the third week of the New Year. The topics on that day, we will have two. We anticipate a full meeting that day, functional neuroimaging for primary degenerative dementia or mild cognitive impairment and appropriate imaging for breast cancer screening in special populations.

A little background for those unfamiliar with the program. The Health Technology Assessment Program is managed out of the Health Care Authority, a state agency in Olympia. The program was created through legislation in 2006 and it's designed to use an evidence report and a panel of clinicians to make coverage decisions for selected medical procedures or tests based on the evidence of their safety, efficacy, or effectiveness and their value or cost effectiveness. Multiple state agencies that purchase healthcare participate in identifying topics and ultimately implementing policy decisions from this program. They include the Health Care Authority, which manages the Uniform Medical Plan for public employees and the state Medicaid program, The Department of Labor and Industries and the Department of Corrections. Again, implementation is mandatory by these agencies, and they implement what comes out of this program.

The purpose of this program is to pay for what works. We work to ensure that selected treatments that are reviewed, including medical devices and procedures that are paid for are effective and safe. We provide a resource for these state agencies to develop these policies. We develop scientific evidence-based reports on the selected medical devices, procedure, and tests, and we facilitate the work of this committee that makes these determinations.

Our objectives include transparency to minimize bias in the development of these policies, to be consistent, and to be flexible with our processes, and cyclic. We do re-review when new evidence becomes available that might change existing policies.

A very high level view of the process—topics are identified primarily by the state agencies, but anybody may nominate a technology for review. Ultimately, the director of the Health Care Authority has the authority to select technologies for review. Once they are selected, they go into a project plan that involves contracted reviewers who write the systematic reviews. There are multiple public input points at each of these steps, and then the reports are brought to this meeting where the committee deliberates and makes a determination. Following this, the agencies are charged to implement decisions from the program.

The primary questions we look at are, is it safe, is it effective, and does it provide value with improved health outcomes? Again, we highly value and are required to be transparent. We seek the best evidence for these systematic reviews, and the decisions of this committee, as practicing clinicians, make their decision based primarily on the evidence available in the reports.

The clinical committee decisions must give greatest weight, as I said, to the most valid and reliable evidence based on objective factors. For evidence consideration, this includes the sources of the evidence, the empirical characteristics of the studies or trials, on which the evidence is based, and the consistency of the outcomes. Additional factors might include how recent the information was developed, how relevant it is to the questions being asked and any assessment of bias in the literature.

Our topics for the coming year include today's topic on screening for osteoporosis, again, the functional neuroimaging for primary degenerative dementia or mild cognitive impairment, appropriate imaging for breast cancer screening in special populations followed by testosterone testing in March of 2015, and then in May imaging for rhinosinusitis and a review of bariatric surgery in May, as well.

There are many ways to participate in this program. We have a website where all of the information draft products and final products are published. Anyone may join our stakeholder list, which is the best way to stay apprised of what is going on in the program and when public comment periods are open, and anyone is welcome to comment on proposed topics, draft key questions, draft and final reports, and draft decisions or attend these public meetings. All meeting materials are posted on the web and released at least two weeks prior to the meetings, and anyone may present comments today or at other public meetings before the committee. Again, anyone may nominate or provide a petition for review of any technology, and there is some contact information. Thank you.

Craig Blackmore: Thank you, Josh. So, next item on the agenda is review and approval of the previous meeting business. Our last meeting was on July 11th. It was a telephone meeting, still open to the public, but a telephone meeting, and really the purpose of that meeting was to finalize the decision, the draft decision on proton beam therapy. The minutes for that meeting are in the packet handout and have been distributed or on the web, etc. So, I would solicit discussion of the minutes or I would solicit a motion to approve.

Woman: [inaudible]

Man: Second.

Craig Blackmore: So, I could have a show of hands, approval of the minutes from the meeting of July 11?

Josh Morse: It looks like nine approved. Ten.

Craig Blackmore: Alright. Previous business meetings are approved. So, we will now launch into the next topic, which is screening for osteopenia and osteoporosis, and we have... we have rearranged the order of things a little bit. We got a lot of feedback from stakeholders in this process, from participants, from members of the public, and as a consequence, we have just shifted things a little in that we are going to have the Washington State Agency report before we go to the public comment period. Are we ready for that?

Josh Morse: Yes.

Charrisa Fotinos: Good morning. Can everybody hear me alright? I'm waiting for the slide advancer. Thanks. Good morning. My name is Charissa Fotinos, and I am the Deputy Chief Medical Officer at the Health Care Authority. I am going to spend the next few minutes talking about our review of screening and monitoring tests for osteopenia and osteoporosis. I'm trying to figure out which way to look. I guess I'll look straight ahead.

In terms of the concerns related to this topic, in terms of safety, the agency medical directors rated this as low to medium, both considering concerns related to the safety of the procedure, as well as medication side effects. Efficacy was of medium concern in terms of the ability to accurately predict osteoporosis, and then costs were medium to high. Last year, we spent about \$680,000 for DEXA Scans and a few other tests related to bone density screening. From a medication perspective, teriparatide was the sixth most written specialty drug in the public employee benefits plan and 26th most expensive cost wise.

Osteoporosis/osteopenia are generally defined by bone mineral density and grams per meter squared, either at the hip or lumbar spine. The diagnosis of osteoporosis can be made in an adult with a hip or vertebral fracture in the absence of major trauma and bone loss and fracture risk increase with age. Because this is a discussion... I am sorry. This is delayed. Because this is a discussion on screening, I wanted to just take a moment and review some of the

principles of a good screening test. In order for a test to be a good screening test, you want a condition that carries an important public health problem, has a significant burden. You need a valid, reliable test that can find the disease in its earlier asymptomatic stages. You want an intervention or treatment that can work. The test should be cost-effective and the benefits should outweigh the harm. So, as we go through this, we will touch on these different criteria.

Key questions, which will be reviewed in more detail in the upcoming presentation, is there direct evidence that screening for osteoporosis and low bone density improves health outcomes, management decisions or patient choice both at the individual or population level? What is the minimal interval required to detect transition from normal or low bone mineral density to osteoporosis to assess treatment effect? And what is the number needed to screen to prevent one fracture, and is there a difference between age, sex, and other risk factors in that number needed to screen? Are bone density tests safe, and what are potential downstream effects, and what are the costs and cost-effectiveness of screening and monitoring?

Burden of osteoporosis; about 9% of adults over 50 have osteoporosis, about 48% have osteopenia, and this is from NHANES data from 2005-2008. It accounts for about 0.5% of all office visits annually, about 2.5 million, not quite 2% of hospitalizations. These are in adults only, these figures. About 180,000 nursing home admissions, hip fracture specifically, is associated with an increased mortality at one year and ranges with estimates from 8% to 36%, and this is a bit dated from 2007, but the Partnership for Prevention ranked osteoporosis 21st out of 25 preventive conditions in terms of clinical preventive burden and cost-effectiveness. If you screened and treated everyone for osteoporosis, it would rank 21st out of 25 and for context, tobacco use and immunizations are ranked one and two.

Looking at our agency experience in terms of patients with osteoporosis, this reflects the Public Employee Benefit Plan, and not surprisingly you see that over this three-year period, the majority of people diagnosed with osteoporosis were women and the peak age was around 65, which again, isn't surprising.

I show this next slide. This is reflective of Medicaid data and what you can see is there is a much larger peak in younger ages, and this is reflective of the number of severely-ill children who have either cerebral palsy or other conditions that have them immobile and with increased osteoporosis and osteopenia reflecting there.

Testing, there are multiple validated instruments that exist for testing, both with and without direct measurements of bone mineral density. There are different scores that can be used to predict fracture risk. The standard of care is to measure bone density with a dual x-ray densitometry, or a DEXA Scan. In addition to the actual measurement, generally two scores are given; a T-score, which compares the results to young adults, and a Z-score, which compares the results to age-matched referenced population. These scores vary somewhat by machine that they're done on. Technologies other than DEXA scan exist, but really they're not routinely used, in part because a lot of the standards are built

around the DEXA scan and RCT methodologies and ultrasound methodologies that also allow for bone mineral density evaluation. Bone turnover markers are available and accurate but really not used in regular clinical practice, more research settings.

How do the fracture risk tools do in comparison to bone mineral density? On the left where that big arrow is, those two separate graphs represent ages 65, 70, and 75, and the fracture risk is on the upward axis and you can see based on those ages in a person with no risk factors at those ages. Their fracture risk over the next ten years raises from 1 to 4%. In those same ages with one risk factor, for instance smoking, their fracture risk is graded and goes up a little bit. To the right are all tests where bone mineral density scores were included using the same tool. So, what you can see is that the... the risk is graded over age for people with bone mineral density T-scores of less than 1 or less than 2, the FRAX tool, which is what is used here are pretty approximate. If anything, it overestimates the fracture risk, but when you get into lower bone density scores, such as less than 2.5 and the FRAX tool itself underestimates the risk a little bit.

This shows the distribution of bone mineral densities in 100 women at different ages, so at 35, 55, and 75. What the purple figures show are the number of people who, in the next 10 years at that age group, would be expected to have an osteoporotic fracture. So, again, understandably, the... the number of women over that time from 35 to 75 who have an osteoporotic fracture over 10 years increases, but what I would point out in this slide is that if you look at the number of women with osteoporotic fractures between 0 and 2.5, a T-score of 2.5, there is still a significant number, suggesting that not all women who have osteoporotic fractures do so when their bone mineral density is less than 2.5, suggesting that it isn't a perfect test to pick up everyone at risk.

Who should be screened? The U.S. Preventative Services Taskforce recommends women over 65, women less than 65 years if their 10-year fracture risk is greater than 9.3%, which is what a risk of a 65-year-old woman would have, and this is using the FRAX tool. Most other societies agree with these recommendations and recommend screening for men over 70 years or those younger with risk. Follow-up testing is recommended anywhere from everyone to five years and then for persons at particular risk, chronic steroid therapy or other conditions vary by the recommending body, specifically the U.S. Preventative Services Taskforce doesn't make recommendations regarding screening for men.

The harms of testing – the radiation dose exposure is minimal. It's about equivalent to a daily dose of background radiation. An x-ray, as you can see, is about six times higher. There is something called a least significant change value for each machine. There is some variability in the machine and the repeat tests, and generally if a change from time is significant enough percentage-wise, then that's considered a real change as opposed to just a variability of the machine, and they are fairly precise, between 1 and 2% variation in terms of precision for the different machines.

Treatment – this is from a recent Annals of Internal Medicine article that looked at a comparative effectiveness review of information regarding treatment for osteoporosis. Women over 65, the number needed to treat to prevent one vertebral fracture is between 60 and 89. This is across medications, and then the number needed to treat is 50-67 to prevent one hip fracture, and these were both over one to three years, and for some context, in people having a heart attack and given aspirin, the number needed to treat to prevent a cardiac-related death in five weeks is about 40, and if that person is given thrombolysis within five hours, 100 people needed to be treated in order to prevent a cardiac-related death, so reasonably good numbers needed to treat, depending on your perspective.

Unclear effects of treatment on osteopenia or prevention in patients with secondary risks and the data across the studies for men was sparse. There aren't really any comparative effectiveness reviews. These were really done kind of just comparing one to the other. Risks of medication, I think most folks are familiar with the hot flashes, GI symptoms, thrombosis. There is a lot of mention of subtrochanteric femur fracture. That risk appears to be mostly related to bisphosphonates and is somewhat dose and duration dependent.

What do folks recommend in terms of repeat testing or monitoring? Most organizations recommend repeat screening every two years. The Oregon HERC standards are result-based. If a person has a normal BMD, they recommend a repeat screen in 15 years, mild osteopenia, which they define as a T-score less than 1, excuse me, -1 to -1.49 every 10 years, moderate every four, and severe osteopenia, which is a... or osteoporosis, which is a T-score less than -2 every two years. Once a person is on medication therapy, they say there is insufficient evidence regarding recommendations for serial testing.

The current state agency policies are that these are covered by Medicaid, Uniform Medical Plan, and L&I. Department of Corrections requires prior authorization.

This is showing the numbers of tests and costs over the Public Employee Benefit Plan over this two-year period, or three-year period. You can see that the number of members over that three-year period slightly increased to 2.3% and the number of members with osteoporosis decreased, and that... I'll comment more on that in a little bit.

Looking at the payment profile and numbers for Medicaid, I show this slide really only to point out where the circle is, is that the number of patients in fee-for-service screened for osteoporosis is declined by about a third, but what you can see is the, the number of patients with managed care program, screen has gone up by 60%. That just reflects a large shift in numbers over this time period of folks being covered in fee-for-service, as opposed to managed care programs, so, not just a reflection of the population shifting coverage types.

Reimbursements are listed here. You can see that for the axial densitometry, PEBB pays about \$140, L&I about \$85, and Medicaid \$30.

When you look at the diagnosis type for the reasons, which DEXA scanning was used, you can see that across the Public Employee Benefit Program, it's largely related to osteoporosis conditions whether that's coded as osteoporosis or senile osteoporosis, and I believe there should be another line underneath that's not showing. The diagnoses are a little... OK. We good? OK. So, looking at the Medicaid diagnoses, still a fair percentage related to diagnoses for osteoporosis, but you can also see a larger section listed diaphysitic hypertrophy and polychondritis, so a slightly different diagnosis pattern.

Looking at... in detail a little bit more of the diagnoses in the Public Employee Benefit Program, you can see that for first DEXA tests on the left, most often they're done for screening, often diagnoses of disorders of bone cartilage or asymptomatic menopausal status and repeats pretty much the same diagnoses, not anything really particularly surprising. Medicaid is slightly different. I outline the acute myelocytic leukemia just because in that younger age group, there are different reasons for which these screens are done related to side effects of treatment.

Private payer examples – AETNA covers when the test is deemed medically necessary for members with risk factors, and they outline those. They cover it for men over 70 years or with a history of fragility fractures. Oregon HERC kind of reviewed that earlier, women over 65 or men or women if their 10-year risk is over... 10-year risk is over 10% and Group Health and Regence, there is no general coverage policies.

CMS doesn't have an NDC specifically for it, but they do list in... in one of their pieces... one of their products in 2007 these criteria that they are covered every 23 months for any one of the following conditions, and you can see they are women who are estrogen deficient, have vertebral abnormalities suggestive of osteoporosis, people on high-dose steroids for a period of time, folks with hypothyroidism or someone who is being monitored to assess therapeutic benefit.

Looking at the evidence that will be presented in much more detail shortly, looking at the effectiveness of DEXA scans to prevent a fracture in a middle-aged adult and folks over 65 or any subgroup, the findings favor screening, but the upper confidence interval limit is close to 1, and the quality of evidence was low. To prevent fractures in people taking medicines associated with osteoporosis, there were two subgroups of men in which there was found to be some support for this. Again, the evidence in those studies was low. Does it change clinical management? In the two subgroups of men taking ADT or high-dose corticosteroids for ulcerative colitis it, in those studies, showed that more men were likely to be treated. So, in that sense perhaps it influences clinical management. Does screening change patient behavior? There was a population-based community study in which they screen people and... and for a year... folks, once they got their results, took a little bit more vitamin D and calcium, so perhaps.

Frequency of screening, depending upon... if you look at the range of recommendations as every... a little over one year to every almost 17 years.

Serial monitoring, really insufficient recommendations due to lack of evidence. Benefit versus harm, it is a safe technology. There is some concern about population level testing and medication effects, and... and this is pretty good quality evidence for the medication effects. Cost-effectiveness, again, you'll hear this more detailed but two different studies looking at women older than 55 and 65 in both the U.S. and Canada suggested that it is cost-effective at a threshold of willingness to pay about \$50,000 for one quality-adjusted life year.

Number needed to screen are kind of all over the place. If you look in the one study, which was a nonrandomized study on the left by age group, you can see that the number needed to screen to prevent one hip fracture over five years in the oldest age group there is 238 and the younger age groups 55-59 for example, quite high. In a systematic review that looked at adults over 65, the number needed to screen over five years were much lower. So, again, quite a discrepancy. Adults over 85 that were needed to screen over five years was seven. So, quite a... quite a variation.

So, given this information, what are the uncertainties? It isn't entirely clear who should be screened, whether it's age-based and/or fracture risk-based using a particular tool. How often should screens be repeated, as part of serial screening? There was a wide range, again, suggested. What's the optimal interval for monitoring once on therapy, because women have osteoporotic fractures on therapy even if their bone mineral density changes or doesn't change? As there is insufficient evidence regarding screening and testing for men, what particular recommendations should be made related to them, and the prevalence of treatment estimates for us at the Health Care Authority are difficult to determine for current HCA clients, because we have that snapshot of only three years. Physicians may not always list osteoporosis as a diagnosis during that time period if they're not screening someone and they're treating their diabetes or hypertension. So, it's really hard for us to say what exactly the burden is, in terms of prevalence in our programs.

So, our recommendations related to this are, cover with conditions. Women over the age of 65 or younger women with a 10-year fracture risk of greater than 9.3%, which is in line with the U.S. Preventative Services Taskforce recommendations to be covered. Serial screening shouldn't be covered more often than every two years and in low-risk persons could occur as infrequently as every two... 10 years, excuse me. Once treatment for osteoporosis has begun, serial monitoring isn't indicated, and in the setting of a fragility fracture, a DEXA scan shouldn't be obtained to confirm the diagnosis of osteoporosis. Any questions?

Seth Schwartz: Can you go back to the slides that... the graphs for public employees and Medicaid, and do you have any comment on why there are so many diagnoses of hypertrophy polychondritis in that Medicaid Group?

Charissa Fotinos: We... we were trying to figure out exactly what that meant and it wasn't entirely clear. The only thing I can think of is, because, as you saw that peak in the sort of 7 to 20-year range in that younger group, I think there are a lot of underlying medical conditions, and so rather perhaps than the underlying medical

condition, they are... they are coding fragile bones or something in... in that instance, but we pondered, and it was hard for us to tell exactly what was going into that bucket, but I suspect it is a reflection of that younger age group.

Charissa Fotinos: Alrighty, I guess I am done. Yes, sir.

Richard Phillips: Yes, could you give an estimate of the average cost per patient for osteoporosis, for patients who are treated?

Charissa Fotinos: Not off the top of my head. That is something that we could certainly find out for you. Once... once the diagnosis is made, treated over a period of time do you mean?

Richard Phillips: Yes.

Charissa Fotinos: With, with medications? OK. I... I don't know that off the top of my head, but we could certainly try to find that information.

Craig Blackmore: Can you clarify for us where the 9.3% comes from?

Charissa Fotinos: That's the, if you use the FRAX tool, at the age of 65 without risk factors, that's what the 10-year risk of an osteoporotic fracture is.

Craig Blackmore: Thank you.

Charissa Fotinos: And that's what U.S. Preventative Services [inaudible] says.

Michelle Simon: On slide 19, you have two CPT codes for the DEXA scans. Don't... are those commonly run together? I think they are. Are, they aren't really run separately, are they?

Charissa Fotinos: Which, I'm sorry, I apologize?

Michelle Simon: Slide 19. It's the current agency fee.

Charissa Fotinos: No. Generally, Margaret are you here?

Craig Blackmore: I can help with that if you like.

Charissa Fotinos: Yes.

Craig Blackmore: So, let me introduce our clinical expert, Dr. Christopher Shurhart, and we... we usually do this a little later, but we will do it now because we need your input and so, Dr. Shurhart is here to help us understand the clinical context better, because the committee members may or may not be... have individual skill in the... in the particular clinical area we are studying. So, Dr. Shurhart's role is to be here to help with clinical context, not interpretation of the evidence. That comes from the evidence vendor and the committee members, but this is obviously a situation where we need to understand the clinical context. So, please.

- Christopher Shurhart: So, um, these tests are sometimes run together. These are two separate CPT codes. The axial bone density test is testing at the spine and the hip, and that's about 90% of scans that are run in general, and the 77081 is the distal forearm that's used as an alternate site about 10% of the time.
- Richard Phillips: I had one more question. In your presentation, there wasn't anything about the burden of... the fracture burden and the cost of fracture burden associated with osteoporosis. Did you put that at all in this determination?
- Charissa Fotinos: It wasn't... it didn't include cost as much from a burden perspective as... as numbers of burden. But again, related to your question of cost in terms of treatment and burden, that's something that we can... I can work on while other folks are speaking. It should be available.
- Craig Blackmore: So, we are going to move on just to be somewhat true to the agenda but there will be more opportunity later if we have other questions, I am sure. We are... it is now 8:40, and I want to try to respect the time we have laid out for the public comment period, particularly in case there are people on the phone who are expecting to have the opportunity to... to address the committee. So, we are in the public comment period, and do we have, what have we got, Josh?
- Josh Morse: We don't have any pre-signed up comments and Christine, do we have anybody signed up?
- Christine Masters: We don't.
- Josh Morse: So, we should check the phones, and I should remind everybody, we are recording this meeting, and if you could please use the microphones and state your name when you speak, thank you.
- Craig Blackmore: Strength of evidence, we are in the public comment period, and we have un-, unmuted the phone. So, if there is anyone who has called into the meeting and wishes to address the committee, if you could please indicate now. Alright, is there anybody in the audience here who, getting some shaking heads? So, OK, it... we will revisit the public comment issue a little later in case somebody tried to call in or come later and wanted to be in that window, but since there is no current public comment, we will... we will move on and we will launch into the evidence report, and I will warn you that I may... I may interrupt the evidence report to double check on public comments, as we get to the end of that window, but.
- Teresa Rogstad: OK, good morning. My name is Teresa Rogstad. I go by Teri, and I am with Hayes Incorporated. We were the contractor assigned to research this topic. My first couple of slides define the acronyms that are used often throughout the presentation. I would also like to point out that the report and the slides often refer to the 2010 Nelson Review. This was a systematic evidence review conducted under the offices of the Agency for Healthcare Research and Quality, and it served as the background paper for the current U.S. Preventive Services Taskforce recommendations on screening for osteoporosis.

I will review some of the background, yet you have already gotten a good review of that from the previous presentation, defined the rationale behind this report, and what our search results were. Then, I will launch into the findings and end with a brief review of practice guideline and payer policies, and then wrap things up.

So, as you have heard previously, osteoporosis occurs at about 16% of women over the age of 50 years based on the most recent survey conducted by the CDC. It affects about 4% of men in that age bracket, low bone mass is more common. Low bone mass, or osteopenia, is important because actually most fragility fractures occur in people who have osteopenia, not osteoporosis, according to the strict definition.

I'm going to go through these slides pretty quickly, because it is, it is review. This slide summarizes the definitions and cutoff points for osteoporosis, depending on age group. There are several different terms that are used to describe osteoporosis-related fracture. Lifetime risk in white women is pretty high, and the economic burden in the U.S. is also high. Hip fractures are associated with the greatest morbidity and mortality when it comes to osteoporotic fractures.

The Nelson review that I referred to before identified 14 tools for predicting the risk of osteoporosis and another 11 for predicting the risk of fracture. All of these tools were externally validated. The fracture prediction tools may or may not include bone mineral density as one of the components. The review didn't make a judgment on which tool, which tools were considered better than others. They did comment that the simpler tools seemed to work about as well as the more complex tools. The fracture prediction tool that is mentioned most often in the literature is called the FRAX. It was developed by the World Health organization. It can be used with or without BMD scores, and it was the basis of the calculations behind the current USPSTF recommendations. Those numbers at the bottom of the... of the slide can be interpreted as follows: The accuracy of the FRAX tool for predicting whether or not a hip fracture is going to occur was correct in 65-81% of the time in the studies reviewed, that were listed in the Nelson review.

This slide lists the components of the FRAX tool. If femoral neck bone mineral density score is available, then the button for secondary causes turns off. If bone mineral density isn't available, that button stays on, and it will still compute a risk. There is an online calculator available and one of the extra slides at the end of the presentation shows you what that looks like.

So, for treatment of existing osteoporosis, the nonpharmacological treatments of supplements and exercise haven't been shown to be effective, even though they are effective for preventing osteoporosis. The practice guidelines are very consistent in defining, the way they define the threshold for offering osteoporosis medications. They would be offered if one of the following three situations applied. The first would be the existence of a clinical or radiographic fracture of the spine or hip. Secondly, treatment could be offered on the basis

of a T-score that was -2.5 or lower, and that could apply to measurements at the hip or spine, lumbar spine. Medication might also be offered if there was osteopenia plus either a 10-year 3% risk of hip fracture or a 10-year 20% risk of a major osteoporotic fracture, and major would be spine or hip. The efficacy of osteoporosis medications has been established for postmenopausal women for several different classes, but it hasn't been demonstrated for men.

The USPSTF updated their recommendations for screening in 2010, and they currently recommend that all women over the age of 65 be screened in the absence of risk factors, and for younger women, screening is based on the equivalent risk profile of a 65-year-old white woman without additional risk factors, and as was pointed out before, that computes to 9.3% risk of a major osteoporotic fracture over the next 10 years, according to the FRAX tool.

The taskforce declined to make a recommendation for men or to prescribe optimal screening levels, because of a lack of evidence. So, the background report by Nelson and colleagues that supported the USPSTF recommendations looked for but didn't find any RCTs designed to assess the effectiveness of screening. The authors of the report concluded that it was still valid to make a recommendation based on two findings: 1. The fact that there are reliable tools for predicting the risk of osteoporosis and also for assessing fracture risk. 2. The second rationale was that there is effective treatment, at least in postmenopausal women, but the taskforce recommendation leaves a number of unanswered questions, and these were the impetus for the current report. We were asked to look for additional or new evidence regarding the impact of screening, the previous systematic review only looked for RCTs, so we... we also looked for other types of controlled studies and any new RCTs. We looked for new or missing evidence on optimal screening or monitoring intervals, and for evidence that would pertain to other populations, such as perimenopausal women or individuals with osteo-produced... osteoporosis-inducing medical conditions. We also looked at cost.

The PICO for the report restricted the population to adults and specified that the intervention would be DEXA scanning, since that is the standard technology for measuring bone mineral density. Health outcomes were of interest, but so were intermediate outcomes, such as clinical management decisions and patient behavior.

I will not reread the key questions, but they are available in... in the full text version on these two slides.

Our searches yielded 10 studies that met our inclusion criteria for providing direct evidence regarding the key questions. We found a small quantity of evidence regarding the effectiveness of screening, but nothing regarding the effectiveness of monitoring or serial testing. Similarly, we found two longitudinal studies that shed light on the appropriate interval for screening but nothing of that sort... of that nature for treatment monitoring. We converted the event rates from three of the screening trials to numbers needed to screen, and we also took advantage of an NNS analysis in that 2010 Nelson review. No direct evidence regarding the safety of screening, per se, and we chose two

economic evaluations that had the most comprehensive models. They both dealt with screening in older women. Hayes' quality assessment methods align with the grade system.

So, moving on to the findings, what I am planning to do is show a summary slide for each key question and then follow that up with slides that present the quantitative results of the individual studies.

We found that screening may reduce fracture risk in middle-aged or older adults and may be more effective with increasing age. The evidence also suggested that screening may reduce fracture risk in individuals who are taking osteoporosis-inducing medications and may increase ineffectiveness with greater intensity of exposure to those medications. We considered all of this evidence to be low or very low quality and those ratings take into account the consistency of findings, the quantity of data, and the risk of bias in the individual studies. We also found low quality evidence suggesting that prescription of osteoporosis medications and supplementation increased, as the result of a screening program, but the studies measuring the effect on patient behavior showed minimal or no effect. We didn't find any evidence regarding the effectiveness of treatment monitoring or population-wide impact.

So, for a little more detail, two studies assessed the effectiveness of screening in older populations, middle-aged to older. The Kern study enrolled men and women who were at least 65 years of age and followed them for five years. They computed a hazard ratio, which is a form of relative risk of 0.64 that suggests that screening reduces the risk of fracture by a relative 36%, but you will see that the confidence interval is pretty wide and the upper bound reaches almost to 1, the null value. So, that tells us it is possible that screening actually had no effect. The Barr Study was a randomized controlled trial, and they enrolled only women who were considerably younger than the population in the Kerns Study. The intent to treat hazard ratio suggested a risk reduction of about 21%, but that was a non-significant estimate. The estimate was significant only in the per protocol patients that is the patients who complied with the screening program.

If we look at those same two studies, there is a hint that screening effectiveness increases with advanced age, but this would be considered very low quality. The first observation would be based on the subgroup analysis in the Kern Study. They stratified their analysis by age, and the only significant relative risk reduction was in individuals who were at least 85 years of age. So, that suggests screening increases, the effectiveness of screening increases with age. You could also make a comparison between the results of the two studies. If you look at the estimate for women that is actually what should be read rather than overall. So, if you look at that 0.61 for women who are at least 65 years age... of age that suggests a greater effect than the 0.791 for the younger women in the Barr Study.

Two studies that happened to only enrolled men suggested that screening reduces fracture risk in individuals taking high-risk medications. The first study enrolled men being treated with androgen deprivation therapy for prostate

cancer, and the second study included men with ulcerative colitis who were taking corticosteroids.

It looks like the findings go in the opposite direction, but that is because the first study compared the control group versus the screen group and the second study went the other way around. One of those studies did a subgroup analysis and found that there was a statistically significant benefit of screening only in the subgroup that had a high exposure to the corticosteroids. That result suggested a 72% relative reduction in risk of fracture.

Three of the screening studies looked at the impact on prescriptions for medications and supplements, and they all found a positive effect. The difference in prescription for these treatments ranged from 6 to 16 percentage points. In the Barr Study, the women in the screening group only who had a low bone mineral density result, for those women, the investigators sent a recommendation to their GP's that hormone replacement therapy be offered, but in the other two studies, there was no active promotion of any particular treatment protocol.

Two experimental studies looked at the impact on patient behavior. They found that calcium intake or exercise might have increased a little bit over a one-year period, but the findings were generally statistically nonsignificant, and since they only followed patients for a year, it is uncertain whether any meaningful change in behavior beyond that occurred.

So, for question 2C, which had to do with the minimum interval for screening and testing, we found nothing regarding the appropriate interval for monitoring of osteoporosis treatment, and we found nothing that applied to young populations or perimenopausal women or individuals who were selected on the basis of risk factors other than age, and we didn't find any controlled studies comparing screenings strategies, but what we did find were two longitudinal studies that were designed to estimate how long it would take individuals with normal bone mineral density to reach an end point that would suggest the need for treatment and taken together, those two studies provide what we considered to be moderate quality evidence that repeat screening generally doesn't improve in estimation of fracture risk for at least several years after the initial screening. Exceptions to that would be the very elderly who had substantial osteopenia at the time of the previous screen.

So, I will go into a little more details on those studies. The first one was conducted in Australia and followed men and women who were at least 60 years of age for an average of seven years. At the end of that time, the investigators took their data and they calculated how long it would take individuals to reach the point where they had a 20% 10-year risk of osteoporosis and/or any fracture. That... that should read any fracture rather than clinical fracture. They stratified their analysis according to five-year age groups and five different categories of T-score at the previous screen. The study reports a lot of results and, by the way, I forgot to mention that at the end of the use table where the committee is seated, there is a set of all the studies that we used as evidence for the key questions. So, this Frost Study is... is in that set. The data

that I have chosen to put on the screen was an attempt to show you which groups of people could go the longest without being screened, according to this study, and which groups would need to be screened again pretty soon. So, if you look at that third set of data for women, longest, what that suggests is that for women who were first screened at age 60 and had a perfectly normal T-score, they wouldn't reach that 20% 10-year risk of osteoporosis or fracture for an average of 14 years. The authors of the report suggested that the lower bound of the confidence interval be used as the clinical guide. So with that guidance, women in this group wouldn't be screened again for another 13 years, but at the other end of the spectrum for women who were at least 80 years of age at the time of the first screen and had a T-score of -2.2, which is getting pretty close to the threshold for osteoporosis, the findings suggested that they should be screened again in a couple of years. The intervals were a little bit longer for men.

Putting the Frost findings in other words, they suggest that repeat screening, more frequently than two years wouldn't have clinical utility for any individuals and repeat screening more frequently than three years would have utility only for elderly adults with substantial osteopenia at the time of the initial screen, and there is some additional detail presented there to show which groups that apply to.

The other study had similar findings. The Gourlay Study was conducted in the U.S., and this study was the basis for the Oregon HERC's recommendation regarding screening intervals. They enrolled only women and the women were all at least 67 years of age. They were followed for an average of eight years, and the model in this study looked at how long it would take for 10% of women to develop osteoporosis or to have a major osteoporotic fracture, or to start undergoing treatment for osteoporosis. They stratified their analysis according to baseline T-score. Those categories for osteopenia were arbitrary. They were created by the investigators. What they found is that women who had a normal or mildly... a normal T-score or a score that suggested mild osteopenia at the first screen, they wouldn't reach those study endpoints for about 17 years, but for women with moderate or advanced osteopenia, according to the authors' definitions, they would reach one of those endpoints quite a bit sooner but still longer than a couple of years, one year for advanced osteopenia.

In addition to these longitudinal studies, we found a reference to a lot of studies showing that change in bone mineral density is actually not a very good predictor of change in fracture risk. This has been found to be true both in screening populations and in people being monitored for osteoporosis treatment. A smaller number of findings had found... reported similar results for individuals who had discontinued osteoporosis treatment or had other kinds of risk factors besides age.

The number-needed-to-screen data were pretty disappointing. For older adults, what the... what the evidence suggested is that the number needed to screen may diminish with age, and you would need to screen more individuals to prevent a hip fracture than to prevent any osteoporotic fracture over a given time period, but there was very serious inconsistency in the findings for older

adults. So, we considered this evidence to be of low quality and very low quality for men, because there were so few data.

We were also able to take event rates from the two studies looking at men who were on high-risk medications and convert those to numbers needed to treat, but there was only one study per medication, and we weren't able to determine whether the number needed to screen is dose dependent. So, we considered that evidence to be of very low quality.

So, going into a little more detail, the current study...

Craig Blackmore: Teri, I am sorry to interrupt. Before you go into that detail, can I just get Christine to check the phones one last time?

Teresa Rogstad: OK.

Craig Blackmore: We... it is an open public meeting, and we want to make sure there is opportunity for people to provide input if they wish to and because we only checked really right at the beginning of that time, they would have been expecting. Go ahead. I want to make sure we haven't excluded anybody. I don't think we have, but, sorry it is a little disjointed, but we will...

Donna Fiorentino: So... this is Donna Fiorentino on behalf of the International Society for Clinical Densitometry, and the National Bone Health Care Alliance, and we would just like to reserve the right to respond at, you know, very points during the... the presentation today.

Craig Blackmore: So, this is the public comment period, and we would...

Donna Fiorentino: Mm-hmm.

Craig Blackmore: ...definitely welcome your comments at that point, and we can allow up to five minutes, and... but then we will be closing the public comment period. So, do you wish to provide any information to the committee?

Donna Fiorentino: Yes, just a... a few things. First, we appreciate the opportunity to... to provide this information. We did file a... a statement on behalf of our organization earlier, and just to reiterate a couple of things. First, there was a question earlier on about the cost of medications, and we would just note that many bisphosphonates now have gone generic in the last few years. So, the cost of bisphosphonates per month now is... can be \$4 to \$5 per month, so extremely inexpensive, while the cost of a hip fracture is somewhere, for a 70-year-old, it is somewhere in the neighborhood of \$40,000 in the first year. So, just in terms of the cost-effectiveness when you look at those, the generic drugs in particular, there is really a dramatic issue there, and... and the only other thing, I would suggest with regard to the Gourlay Study, there... we... we filed a number of... of objections with regard to the quality of that study, and... and the authors themselves really are cautioned about using the results of that... that study to broad populations, but... but clearly one of the just sort of things that jumped out at you is that Gourlay was based on these... the... the condition that a... that

provided for... blended a group of... of women moved from one classification to another and... and the threshold was when did 10% of the women, for example, move from having osteopenia, for example, to full blown osteoporosis? Physicians would never wait until that or... or under few circumstances would they wait until somebody came to that -2.5 number and certainly to kind of write off 10% of the people with regard to those timeframes is really something that isn't... not something that physicians or our group would... would endure.

Then one other thing in terms of the studies that were considered, in terms of the effectiveness of DEXA testing generally. There were two large studies that were... that were discussed and that we raised. One was the Dell Study, which was the Kaiser Study in California, and the report notes that there were no findings in that study, which is... which isn't correct. In fact, on page 191 of the study, it very clearly says that the average reduction in the hip fracture rate, after five years at all of their medical centers, was 37.2%, which was a really dramatic reduction in... in hip fracture rates, and the other study that we would also point you to was a study by King that was published in Health Affairs. I... I co-authored that study, and that was a retrospective look at women in the Medicare program just looking at... just comparing women who had a DEXA study and women who didn't over a three- to four-year period and again, we found that there was a distinct difference between the women who have a DEXA study and women who didn't, and the fracture reduction was 22% over a three-year period, and that study didn't couple DEXA testing with any other sort of intervention the way that Dell and Geisinger Studies did. So, we would just encourage you to look at that study, as well, in terms of the effectiveness of treatment.

Craig Blackmore: Thank you.

Donna Fiorentino: So, we appreciate the opportunity to... to come and give this point.

Craig Blackmore: OK. Thank you very much. Is there anyone else on the phone who hasn't had an opportunity to speak to the committee? OK. I'm going to close the public comment period and let Christine... OK, and thank you. Teri, sorry for the interruption.

Teresa Rogstad: That is fine.

Craig Blackmore: We will resume.

Teresa Rogstad: OK. So, based on the event rates reported in the Kerns Study, those would suggest that 59 men or women would need to be screened to prevent a hip fracture over five years or, if you limited it to women, only 46, but then if you look at the comparable figures in the analysis done in the Nelson review, it was 238 to 556 for women over the age of 65. We looked at several possible explanations for that discrepancy and couldn't... couldn't explain it. It is pretty surprising because the Kern Study was sort of a real-world study and so you would expect their number needed to screen estimates to actually be bigger than those calculated in the Nelson review, which relied on some assumptions

that might not hold true in real-world practice. So, we really couldn't come to much of a conclusion with those data.

For the two studies in men taking high-risk medications, they estimated 26 to screen to prevent a hip fracture over three years with androgen deprivation therapy and 278 for corticosteroids in a population of men with ulcerative colitis. It is important to remember that there is no absolute value for number needed to screen that is considered good. It depends on the cost of the screening and the cost of... the consequences of screening or not screening.

There was no direct evidence regarding safety, but from the background section of the report, we... we drew some inferences, radiation exposure from DEXA scanning is relatively low. It might be a problem if there were repeat scanning over a lifetime. As with any screening test, there is the potential for inappropriate treatment or missed opportunities for treatment if the test is wrong or if the results are incorrectly interpreted, but we have no actual data on whether that occurs. There are serious adverse events that have been reported with the medications, but they are rare or without proven causality and table six in the report summarizes some pooled estimates for some of those adverse events.

The cost of DEXA scan was assumed to be \$98 in a U.S. economic evaluation that was based on 2010 Medicare rates, I believe, and as you have heard, Medicare reimbursement is considerably lower now. That would have the effect of improving the cost-effectiveness ratio, and then the costs for the populations covered by the Washington State agencies are also listed there.

We didn't find any economic evaluations that we felt used an adequate model for assessing cost-effectiveness in men, but we did select two for cost-effectiveness in women, one conducted in the U.S. and one in Canada. They both used the threshold of \$50,000 per quality adjusted life year, as an acceptable cost utility ratio. They came to similar conclusions, positive conclusions regarding older women, but somewhat conflictive... conflicting conclusions regarding women younger than 65 years of age. It is important to remember that these are modeling studies, so they made a lot of assumptions and took estimates from a variety of data sources. They weren't based on empirical evidence regarding the effectiveness of screening and as we have seen, the empirical evidence that does exist is of low quality. We didn't find any cost-effectiveness analyses in other populations or for screening or monitoring.

The U.S. study compared screening with usual treatment, which was assumed that... which assumed that osteoporosis would be treated only after a fracture occurred. Both of these studies looked at a variety of strategies and selected the one that brought the most benefit but still fell within the cost-effectiveness threshold. So, for this study, the best strategy suggested initiating screening at age 55, treating if the T-score fell to -2.5, and screening every five years. So, with that strategy, that was computed to cost \$45,450 per QALY.

The Canadian study took more of a public health population perspective. Their best strategy consisted of screening for bone mineral density and then applying

a fracture risk assessment tool and then coupling those assessments with a universal primary prevention program that would be offered to everyone in the screening group. Their incremental cost utility ratio was \$55,300 and a sensitivity analysis suggested that that would like be, actually, less than the \$50,000 threshold.

So, to briefly review practice guidelines and payer policies, AETNA and CMS cover screening with conditions. AETNA has the most liberal policy. The CMS policy doesn't specifically refer to screening in men, but some of the conditions where screening would be covered might apply to men. Oregon HERC recommends screening only for women who are 65 years of age and no risk factors... risk factors or a comparable risk profile. So, essentially the same policy as the U.S. Preventive Services Taskforce. AETNA and CMS cover screening for purposes... or testing for purposes of treatment monitoring, and they will pay for a screen or a test every two years... at least every two years. Oregon HERC recommends the screening... recommends the intervals implied by the Gourlay Study for screening intervals.

We were asked to look at the evidence base for the CMS policy, but neither the previous NCD nor the NCD that transferred the policy to the manual system was accompanied by any kind of evidence analysis.

The practice guidelines, including the U.S. Preventive Services Taskforce recommendation are very consistent in recommending that screening begin after age 65 in women and that screening in younger women be based on risk factors. Some of the guidelines also recommended screening during menopausal transition. For screening in men, among the professional societies, there is a very good consensus that screening should begin at age 70 unless there are risk factors, but the taskforce declined to make a recommendation for men. Follow-up screening is recommended to occur at anywhere from one to five years, no recommendation from the taskforce on that, and then treatment monitoring is recommended for every one to two years until bone mineral density stabilizes.

A few guidelines addressed the issue of screening or serial testing in high-risk populations who had either medical conditions or were taking medications that exposed them to the risk of osteoporosis. Screening was generally recommended and for patients taking glucocorticoids, treatment monitoring, if they are on osteoporosis medications, was recommended for every six months.

So, to wrap up, the effectiveness of screening hasn't been well established, but there is some positive empirical evidence for postmenopausal women and for individuals using high-risk medications, at least glucocorticoids and androgen-deprivation therapy, the effectiveness of screening may be higher in older individuals or with individuals exposed to a higher dose of those high-risk medications. It is supported by two economic evaluations, at least in older women. The longitudinal studies that we found suggested that individuals with normal bone mineral density or mild osteopenia are unlikely to reach a treatment threshold for several years, but as was just pointed out by the public commenter, that is applied to a population. That is... that is applied to the... the

probabilities in a population. There is no direct empirical basis that allows us to define a precise age to start screening or the risk profile that would prompt screening or to define precise screening intervals. There is good consensus among the professional groups as to when to start screening, not... a great deal of consensus about screening intervals.

Regarding treatment monitoring, there was no empirical evidence or analysis of intervals. There is a consensus that it is necessary to determine when treatment has stabilized bone mineral density; however, there is quite a bit of evidence suggesting that the change in bone mineral density isn't a good predictor of the change in fracture risk, and typically medications are discontinued after five years.

So, additional research is needed for all of the key questions. A screening policy would have to be based on inferences that were in turn based on the existence of risk prediction tools and the effectiveness of treatment and the prevalence of the condition, as well as the cost-effectiveness of the screening. So, while you collect your thoughts, I'll take my seat.

Craig Blackmore: So, questions from the committee regarding the evidence report?

Marie Brown: Can we go back to the comment from the... the public comment and could you comment on her interpretation of the study that she said was different than yours?

Teresa Rogstad: I am not... I am not sure we differ in the interpretation.

Josh Morse: Teri, can you use the microphone, please?

Teresa Rogstad: Oh, sure.

Josh Morse: Thank you.

Teresa Rogstad: She pointed out that the... the study estimates how long it would take 10% of women in that population to reach the point where they had osteoporosis or were being treated for it and the point was, would a clinician be guided by that? Would a clinician be attempting to prevent fracture in every patient or would they assess the probabilities of a patient developing osteoporosis in the near term when deciding when to screen again? So, it is sort of a difference... it is... it is the population versus individual patient dilemma. I hope that makes sense. They... another... another limitation to that study is they were looking at the occurrence of a major osteoporotic fracture instead of *any* fracture. So, the intervals might have been a little bit shorter if they were looking for any fracture to occur. They also based the bone... the baseline T-score was based on the lower of a total hip or femoral neck T-score instead of a low score at any site. So, that also would have the effect of length on those intervals.

Kevin Walsh: Can I go back to slide 34, please? So, you... your conclusion was that you couldn't explain the difference in the number needed to screen calculation between those two studies. If you look at the Kern study, one of the things that

I found interesting was that they compared the screening group to the no screening group. The screening group had more education, higher income, better self-reported health, more physical activity, higher cognitive scores. I thought the comparison was a little questionable at all. If you looked at the screening group and compared treatment versus no treatment, what they found was that there was no... there was no statistical difference in fracture rates. So, these are people who had a score that validated treatment and were treated, and there was no difference in fracture rate. So, I thought that was an interesting study but not for the same reasons that you did.

Craig Blackmore: So, I... I had a question about the cost-effectiveness analysis studies that you reported and let me find the right slide here. I guess it is slides 39 and 40 and if... if I heard correctly, the cost-effectiveness models were based on either screening with DEXA versus not treating until you got a fracture, and it seems to me that the appropriate comparison would be screening with DEXA versus using a FRAX or some other tool that is free and readily available that the standard of care would be not to just wait until people had fractures but to use the other information that was available to guide treatment. Can you comment on that?

Teresa Rogstad: Right, that... that was true of the U.S. study. The advantage of that comparison, it gives... it gives you the, I guess, the absolute effect of the screening, but the other one, the Canadian study, did make a comparison more like what you were describing. The comparator was no program, which assumed that there would be some DEXA scanning based on clinician choice and treatment after fracture, but I guess that is the same thing. It is... it is after a fracture, it is after a fracture occurs. So, yes. It would have been better if these studies had been based on... I mean, ideally it... it would have been good if they had been based on a randomized controlled trial, pragmatic trial, where the control group was treated according to customary care.

Chris Standaert: I have sort of holistic question for you on this. Sort of off the last two comments. So, when I think of a screening test, I think of a screening test, I usually think of like, sensitivity/specificity, like false-positive, false-negative, all of these sorts of things that you don't discuss at all and, and you go into sort of effectiveness in sort of treating the... using it as a... as a way to... does it change health outcomes by leading to some change? And if I think of a screening test, I think of, well, if the screening test identifies something and tells me who and who doesn't have a problem, or give me some risk stratification so that then there is an effective treatment strategy beyond that, that will then modify the ultimate health, health outcome. It is really a question of whether that treatment strategy is effective and whether it is effectively applied, and does the screening tool then help you modify your treatment strategy appropriately? I am having a little trouble sorting that out in the way you presented this stuff and... and I think going back to what Craig said, and I can read this, and one question in my head is, so in a bigger algorithm of how you take care of patients, you know, does the DEXA give you information that would reliably allow you to change your treatment to improve health outcomes that is in addition... additional to information you get from a standard history? Does it help you in some way? Is there data that tells me that the DEXA is the thing that is really leading to the change in treatment? Because you are telling me that

just... the other data you have suggested if you just do a DEXA and you tell somebody you have low bone density, that is a motivating factor to get most people to change their health behavior is very poor. So, it is purely the treatment, right? And, and I think what Kevin says also, sometimes when you look at these studies, well people who got DEXA did better, but they are... getting a DEXA is a marker of being engage... could well be a marker of just being engaged with the healthcare system.

Teresa Rogstad: Right.

Chris Standaert: Right? And so I am trying to figure out, does the DEXA by it... what? How does... I am trying to understand how the DEXA by itself is really changing anything that is leading to effectiveness and is that really the thing that is doing this or is the DEXA in the midst of all this other stuff with an effective treatment strategy leading to better health outcomes? I am... again, I am having trouble sorting it out from what you told me. Does that make sense?

Teresa Rogstad: Yes, sort of. I am trying to figure out which to respond to first.

Chris Standaert: So, this idea that... that... so one, you use a DEXA as a way to screen your population. So, a false-negative/false-negative, false-negative/false-positive, sensitivity/specificity in the population and having compared DEXA to just say a FRAX without DEXA, it is curious to me that part of the FRAX actually has a DEXA... has a BM... has a DEXA in it, which is a little confusing to me, but, comparing FRAX without that to FRAX with that to see if they are relatively the same in terms of sensitivity and specificity. Is the bone mineralization data really changing your ability to stratify, and then in the studies you gave us even saying it improves health outcomes, what about it improved health outcomes? What... what... what is the connection between DEXA and health outcome? Is it the treatment that was given to help people stratify? Did it... what is...

Teresa Rogstad: Well, the...

Chris Standaert: ...you... you're making several leaps in saying we go from a sensitivity/specificity question to a... it's effective in improving health outcomes. These are different...

Teresa Rogstad: They are two different things.

Chris Standaert: ...there is a spectrum thing there.

Teresa Rogstad: Yes, yes. There is... there is... there is the accuracy of the test, which isn't discussed in terms of sensitivity/specificity because it is... it is a... it is a risk prediction test. So, usually in, with those kinds of tests you talk about relative risk and I can... while you are deliberating, I can... I can try to find the study that is usually cited showing the... the... demonstrating that DEXA scan predicts fracture risk. It has a strong association with fracture risk, but the impact on treatment would occur because indi... either individuals who are screened were prompted to behave... to adopt more healthy behavior, or they are more likely

to get treated for low bone mass rather than waiting until they have a fracture. That is....

Kevin Walsh: Or, or they were in a different subgroup to begin with.

Teresa Rogstad: ...pardon me?

Kevin Walsh: Or they were a different subgroup to begin with.

Teresa Rogstad: That... that is true. That is true. They are more engaged with the...

Chris Standaert: So, I guess in the, in the studies you have then showing these improved, the two studies you gave us, which aren't... I mean... one other thing about this is, yet again, for something so widely utilized your data is really, you know, you don't get above low quality on anything, which is sort of mind boggling, yet again, but this is what we see, but so in your study, so in these first studies, the Kern Study, right, they use some... if they screen then they use some intervention, I assume, right? Do they discuss the health intervention they used to try to improve health outcome, or do they just say these people got screened, and then we watch them years later, and we didn't institute an intervention? We didn't do anything. We just put them back into the healthcare milieu, and five years later this is what we found.

Teresa Rogstad: Yes... yes.

Chris Standaert: Was it... there was no structured intervention that came off this.

Teresa Rogstad: No, no prescribed intervention, correct.

Seth Schwartz: That isn't true.

Teresa Rogstad: Well, they... they didn't...

Seth Schwartz: They compared, within the group that was screened, they compared people who... who took calcium, multivitamins, estrogen, calcitonin, bisphosphonates. They compared that subgroup of the screened group to the group... to the screened group that took no... that did nothing and there was no statistical significant difference in fracture rate between those two groups.

Teresa Rogstad: That, well...

Chris Standaert: So, I mean you got the... you could get the data, but even if you didn't treat... give them calcium and bisphosphonates or not, you didn't wind up with an ultimate health outcome difference, but what you have is a population where that, in that screened population, they have a different outcome of people who weren't screened, but intervention within the population weren't associated with a difference within people who were screened.

Kevin Walsh: Right.

- Chris Standaert: Such as being screened was a marker, not necessarily a change in behavior because of being screened.
- Kevin Walsh: Right. And there was a difference in the subgroups on a lot of levels. To speak to your question, I would go back to the fracture intervention trial, because what it showed was that they are... so they are calculating difference based on area under the curve, and the FRAX with a femoral neck BMD gave you an area under the curve of 0.71 and a FRAX without a BMD gave you an area under the curve of 0.68. That wasn't a really impressive difference to me. So, I was questioning, how did DEXA become the standard of care if we have a free tool that predicts just as well as a DEXA scan? Like, who sold us that?
- Teresa Rogstad: Well, the FRAX was later in coming. The... the DEXA was well established before the FRAX score became widely used.
- Kevin Walsh: So, because you are used to paying a lot of money for something, you don't want to use it... take it for free?
- Teresa Rogstad: Right. Well... it is just a behavior... it is added to DEXA screening.
- Chris Standaert: Did you happen to look for studies that compared different screening tools and saying that comparing the study, Kevin was just talking about it, that compared FRAX with and without the DEXA data or other screening tools to DEXA, and do they have differential effects or associations with health outcomes?
- Teresa Rogstad: No. That wasn't one...
- Chris Standaert: You only looked at DEXA.
- Teresa Rogstad: That wasn't one of the key questions, but the, the ARC review looked at the tools that are out there and didn't... they didn't draw any conclusions about the comparative effectiveness of them or the comparative accuracy and... or... or do... they didn't do a pooled... they didn't do a meta-analysis of the accuracy estimates of them. So, I cannot really answer that question, but if you look in that study, there is a copy of it in those sets of articles that I provided, and one of the tables shows the accuracy. The Nelson Study 2010. If you look at table one.
- Richard Phillips: Which study is that?
- Teresa Rogstad: This is Nelson 2010. It is called, it is in alphabetical order by author in that set of articles, screening for osteoporosis and update for the U.S. Preventive Services. Table one gives some detail on the different tools. In the far right column are the accuracy estimates across studies, but they aren't... there's no pooled analysis. It is kind of... but keep in mind the top half of that table is for predicting the existence of osteoporosis and the bottom half is for the fracture prediction tools and in that bottom half, three of those, I believe three of those eleven tools use bone mineral density as one of the components, but if you just look at the accuracy estimates, it's... there's no clear pattern when you compare

those three tools that... that add in the DEXA scan results with the others that don't use it.

Chris Standaert: I am sorry. Which page or slide are you on?

Teresa Rogstad: I am on... I am on one of the articles. You know what, we could actually put it on the...

Kevin Walsh: It is page 103 of the Nelson article.

Teresa Rogstad: ...if Christine would like to... we could actually display it.

Craig Blackmore: Alright, so we are... Christine is working on that. So, while she is working on that, are there any other questions, maybe simple questions so we could... maybe not.

Carson Odegard: I have one for Dr. Shurhart, our clinical expert.

Craig Blackmore: Yes, great.

Carson Odegard: The... in the agency report, they said the precision of the instrument itself, the technology is about a 2% difference, comparing different scanners, but then... and I cannot remember where I saw it, but one of the guidelines was that on monitoring, or on tests, retesting that one of the guidelines said to use a different scanner, and not a different tool but a different scanner. Now, can you comment on... is there a large precision difference or is there...?

Christopher Shurhart: There can be a large precision difference between machines. Really, precision is based on... sorry I am looking through someone's head. I am going to go to this side. It is OK. Precision testing is, in my mind, is integral and critical for... for testing over time, because of systematic errors that are part of the measurement system, and precision between two different machines would generally be greater than precision at the same machine with... so patient A on machine X and patient A on machine X at the second visit...

Carson Odegard: Mm-hmm.

Christopher Shurhart: ...the precision of that... of that measurement would be different than taking patient A and moving them to scanner Y...

Carson Odegard: Right.

Christopher Shurhart: ...for a second scan. Does that help you? So, if there was something...

Carson Odegard: Well, that is why I was confused.

Christopher Shurhart: Yeah, it is confusing. I... I missed that but that would be...

Carson Odegard: Why they would want to go to a different machine.

Christopher Shurhart: ...clearly incorrect in my mind and would introduce, it is possible to do, but it has to be done with some mathematics and... and... and a cross-correlation study.

Carson Odegard: Mm-hmm.

Christopher Shurhart: And it is... it logistically is quite complicated, mathematically simple, logistically complicated.

Carson Odegard: OK, great. Yeah, thank you.

Richard Phillips: I have a question for our expert also. Why... why do you do rescreening on patients who are high-risk? If they are going to be on treatment anyway, why is it going to alter anything? Why would you even bother to do it?

Christopher Shurhart: It is an excellent question. I think there are a number of answers, the first of which is, particularly in the environment that we are in, with what people feel they know about bisphosphonates as... as the mainstay of treatment and harmful drugs, there is actually a fair amount of pressure from patients to know if it is 'working' or not. We try... I try to resist that pressure, understanding exactly what you are getting at that, that rescreening isn't necessarily the best way to understand if medication is working, since treatment really is designed to lower fracture risk, and... and ultimately the result of treatment is that nothing happens. People don't have side effects, and they don't break things.

So... so why would we rescreen patients? There really is one factor in my mind that, it hasn't been brought up, and that... there are patients who fail treatment or who we feel fail treatment without fractures and those are patients who have significant decline in their bone mineral density over time and by significant, I mean, it is a statistically significant decline, particularly if we can assure that treatment is being taken the way that it is supposed to, and that is quite a leap sometimes. There are professional organizations, like the International Osteoporosis Foundation, that have done some work, a recent white paper that they did about a year and a half ago talking about what is treatment failure and how do we understand that? Who we should consider treating. So, for instance, one example isn't you have a fracture on treatment, because treatment doesn't prevent all fractures. So, one of the guidelines for understanding nonresponse to treatment is more than one fracture on treatment taken the way it is supposed to be taken. A second is a significant decline in bone mineral density on treatment that is taken the way it is supposed to be taken. So, that is one aspect of serial treatment.

Richard Phillips: So... so that, well that is.... You're basically saying that you have to have the restudy in order to make the... the diagnosis then?

Christopher Shurhart: If, to... to talk about that aspect of treatment failure, yes. You would.

Richard Phillips: So, I would assume, is that a clinical decision based on...

Christopher Shurhart: Yes.

- Richard Phillips: ...criteria. So...
- Christopher Shurhart: It is a clinical decision based...
- Seth Schwartz: And then what therapy is offered to that patient?
- Christopher Shurhart: Excuse me?
- Seth Schwartz: What therapy is offered to that patient who has failed the bisphosphonate?
- Christopher Shurhart: There are a number of other FDA approved therapies that aren't bisphosphonates. They could be [inaudible], denosumab, teriparatide, raloxifene. Any number... there are four other categories of medications that could be offered to the patient that aren't bisphosphonate.
- Kevin Walsh: It seems to me in that situation you aren't talking about rescreening patients, you are...
- Christopher Shurhart: No.
- Kevin Walsh: ...actually talking about follow-up studies, which is a...
- Christopher Shurhart: Monitor, right.
- Kevin Walsh: ...different, which is different than serial screening at every two years or every five years...
- Christopher Shurhart: Correct. For patients who haven't... don't have a diagnosis, right.
- Chris Standaert: But things... using what you said things are also getting a bit confused because you are treating to reduce fracture risk. You aren't treating to alter the ultimate effects of the DEXA scan, the ultimate measurements in the DEXA scan.
- Christopher Shurhart: The primary...
- Chris Standaert: So...
- Christopher Shurhart: ...function of treatment is to lower the fracture risk.
- Chris Standaert: Right. So, defining treatment failure by declining bone mineral density is counter... there's a contradiction there, right, 'cause you aren't using the DEXA to stage treatment. In order to use DEXA... there is no data I saw that says DEXA is a reliable measurement tool of change in bone mineral density over time, as a response to treatment, and treatment is really, in terms of exactly what you said, to reduce risk and change the stratification. So, DEXA would... using DEXA say treatment failed, I don't know how you do that.
- Christopher Shurhart: Well, so...

Chris Standaert: Because...

Christopher Shurhart: ...that's actually based on results of clinical trials showing that subanalysis from clinical trials showing that patients who have significant decline in bone mineral density have overall higher rates of fracture, even while treating.

Chris Standaert: Despite treatment?

Christopher Shurhart: Despite treatment, right. Right, so some of the... some of the underlying issues here isn't all... remember, people...

Chris Standaert: So, the... but then the assumption being that, OK, the bone mineral density is declining, they have a higher fracture risk. So, if we change our intervention, we will effectively change their risk profile again.

Christopher Shurhart: That is their... that is the assumption.

Chris Standaert: That is the assumption. Right. So, I had a question on... just for the evidence vendor, another one, just to keep you thinking, I guess. So, on these Frost studies and stuff, so the Frost and the Gourley studies, if you look at the data and you say, you know, people decline rapidly over age 80 when they have a T-score of less than 2.2. So, one, does a fairly high percentage of the population at age 80 in women have a T-score of that? Is the distribution fairly high and so, if the distribution is sort of, you know, 70 or 80% of the people in that age bracket have that T-score, we shouldn't be doing DEXA's. We should be working... giving them calcium and treating their bone density if it is medically appropriate otherwise, because they... the whole group is in such a high risk, and it was, it was somewhat, when they throw that in with the cloud scatter slide of the... of the... of the agent... state agencies, slide 11, I think it says cloud or fracture risk. It isn't like the only people who break are ones with T's of 2.5. All sorts of people break. So, when you hit that age bracket, it is almost like you're, it is these other things. It is history, it is smoking, it's age, it's BMI. There are really... you wind up with such a high population over 80 that has these risk factors that... I am trying to figure out how the... does the DEXA really help you? Or are you so high up that you are like... the data just suggests that these... we should just treat them, and... and we had this... we had this with sleep apnea, even like... is... sometimes the screening is almost, you know, irrelevant.

Christopher Shurhart: Well, so I am going to jump in here because there are some data that are no... the clinical trials data, again, reanalysis of clinical trials data that are available that answer... that start to get to this question and, once again, the clinical trials data very specifically selected population specific medications, but for the cousin of the... of alendronate or Fosamax called Actonel or risedronate, there are some data out of a study called the Hip Trial, which basically looked at very high-risk older women. These are women with at least a T-score of less than -3.5 or lower with and without risk factors, so very high-risk women, and basically looked at their fracture rates. This was part of a... part of a larger clinical trial. Looked at their fracture rates with and without BMD. I'm sorry, this is an... this is an intervention trial. So, these patients were randomized to

treatment based on either age and risk factors or age and T-score and risk factors, and the outcome. So, it was basically trying to understand how much does BMD really matter, and the ability of... to... the ability to prevent fractures in patients who are randomized without BMD versus those who are randomized with BMD, there was about a 50% difference there in the fracture risk reduction between those two groups. So, the BMD added power to be able to lower the... risk factors alone and age missed 50% of fractures when those patients were treated, so.

Kevin Walsh: But that isn't your point. Your point is, if the incidence is so high in this subgroup of older women, even if you're missing fractures, you should just be treating everybody.

Chris Standaert: And is there a reason why that paper... you didn't talk about that paper, I don't think.

Christopher Shurhart: Well, I think it is a clinical trials level kind of stuff. So, it may not be part... I don't know. You would have to answer that.

Chris Standaert: So, was there a reason, do you know...

Teresa Rogstad: Right, it didn't...

Chris Standaert: ...why, why it ...

Teresa Rogstad: ...come up, because we didn't do a systematic search for treatment trials, and it wasn't... didn't happen to be mentioned in the review articles.

Craig Blackmore: So, what have you got for us on the board here?

Teresa Rogstad: Well, the... this... this was in that ARC review by Nelson and colleagues and let's see if you... the top half of the table is osteoporosis prediction tool. So, let's scroll down to the bottom half, and those are instruments for predicting fracture. Three of them, that would be the... the FRAX tool, the Garvin nomogram and the... correct me if I get this wrong, there is one other, oh the fracture index or SOF. Those three include bone mineral density in their models. The others don't. So, those three are right in the middle of the list and if... if, you know, you can compare the accuracy estimates for those three with the others. I am not sure you can come to a clear conclusion that they are... whether or not they are more accurate. The authors of this systematic review didn't offer any commentary on that.

Craig Blackmore: Any other questions or comments?

Marie Brown: So, was there a difference in the predictive value using a FRAX with or without the... the bone density?

Teresa Rogstad: We didn't find any analysis of that. You do get different... you do get slightly different answers, but we didn't come across any analysis of the comparative accuracy.

- Craig Blackmore: But there is data up here on comparative accuracy.
- Teresa Rogstad: I am sorry. There... there is, you're right.
- Kevin Walsh: Fracture Intervention Trial.
- Teresa Rogstad: So, it is... so yes. Accuracy is 71% with BMD included, 77% without BMD. Those may be... I... that is from this... I am sorry, that isn't FRAX. That isn't the FRAX tool. That is the fracture index tool. So, I am not aware of that type of comparison for the FRAX.
- Christopher Shurhart: So, in the Fracture Intervention Trial they describe comparing FRAX with BMD to FRAX without BMD using the area under the curve, and the difference is 0.71 for FRAX with a BMD and 0.68 for FRAX without a BMD.
- Craig Blackmore: Alright, well let's cogitate on this for a while and take a 10-minute break and return for our deliberation. It is a little before 10:00. Why don't we resume at 10:10, alright?
- I am going to ask the committee members to resume their seats. Can I ask the committee members to return?
- Marie Brown: How long has DEXA scan been around?
- Craig Blackmore: So, I will call the meeting back to order. I think we have the quorum, and the first question is, how long has DEXA scanning been around?
- Christopher Shurhart: So, DEXA scanning in its present form has been around since the middle 1980s. Dual-energy x-ray measurement. Bone density measurement from the outside has been around since the 1960s. Previously, it was a nuclear medicine-based technology and has gone through and this is... DEXA is probably the fourth generation of bone density measurement from the outside. Does that help?
- Marie Brown: Yes, thank you.
- Craig Blackmore: Other questions for any of our inputs?
- Carson Odegard: I have one, Craig.
- Craig Blackmore: Go ahead.
- Carson Odegard: Could somebody summarize how the task force agreed with the 65-year age cutoff, because it doesn't comply with, especially when you look at Frost and Gourlay, I mean, Frost study they... if you take women, just took women not men, if you look at that, there is such a wide difference between the 60- and 80-year-old group in, in who reaches that threshold that they are... or that end point that they are looking at. So, you go from two years to 14 years or something, um, in those two groups. You look at Gourlay, and they are... they're not even screening until 67, and there is 16 years to where they reach

that endpoint. So, I guess my question is, where... where did that number come from?

Craig Blackmore: Teri, do you want to take a shot at that?

Teresa Rogstad: I will give it a shot. Well, the... the Frost and the Gourlay studies were looking at... at... at screening intervals, so, how long you should wait before you do a second screen and the U.S. present... the taskforce didn't make any recommendations about that and it wasn't clear in the background report how they came up with the age 65 cutoff, except that for a 65-year-old white woman and no other risk factors, they have about a 9.3% 10-year risk of major osteoporotic fracture and presumably that was... that was considered sufficient to screen.

Christopher Shurhart: The USPSTF did look at a number of alternative, and this is sort of deep in the wood... in the weeds here of the report on, on I believe, on screening for osteoporosis from USPSTF. They looked at a couple of other models for risk, including one that has been around called the OST and the score model and looked at the discriminatory ability of those. They weren't that much different from the FRAX threshold at 9.3% when... when they used an equivalent to assess a hip BMD at -2.5, and in the fine print, as I recall it, and I... I could be wrong, there is some mention of the fact that the committee felt that the FRAX tool would be the best tool to peg a criterion on because of its more generalized applicability. FRAX was created with 10 large cohorts to create the model and 12 large cohorts to validate the model, and all in all, about 250,000 patients on each side of that. So, my understanding is that it was based a bit on the... the generalizability and the robustness of the FRAX model, but that is all. There... there wasn't any... any other kind of analysis like this, as far as I know.

Kevin Walsh: OK, was that FRAX with the BMD or without?

Christopher Shurhart: That was FRAX with...

Marie Brown: With the BMD.

Christopher Shurhart: ...no. This, because this would have been a criterion. That would have been FRAX without BMD, I believe. I will double check for you, because I can find... I can find the right [inaudible].

Marie Brown: OK.

Kevin Walsh: Thank you.

Craig Blackmore: So, every time we tackle a question, one of these technology assessments, they are different and they are all challenging in their own ways. This... this one is different in the sense that we are dealing with a very common and important clinical and public health issue, and one for which there is treatment that is effective, albeit not perfect, but we aren't asked really to look at the treatment. We are asked to look at how we identify people to use that treatment, whether it is by this DEXA scanning or whether it is by some... something... a model like

the FRAX. We have to understand the treatment, because we have to understand what aspects of the risk identification is important, and to do that, we have to understand what and when the treatment works, but our question is really fairly narrow. It is when do we use DEXA? And really, when does DEXA add incremental value to free, simple, other approaches, like the... the FRAX being the predominant one?

So, it is a twist, and I guess at this point, I would like to get a sense from one or more members of the committee on how it is coming together or where to start from so that we can identify maybe there are some areas that we are pretty confident about and other areas that maybe we need a little more discussion. So, does anybody want to take a stab at trying to put all this into context to get us started?

Michelle Simon: I don't know if I am ready for all that, but I do... I do want to just share some of my thoughts and what I'm... I'm puzzled by and I am struggling with. There is an assumption here that bone mineral density, the measurement of that decreases fracture risk, and I'm not sure that that is actually proven out. I think that the tests that we have here, a DEXA scan, does probably accurately represent bone mineral density, but if you think about bone strength, I mean, there are a lot of factors that would go into it, elasticity, you know, tensile strength. There are many things that would confer that a bone would resist a fracture, you know, when a person falls. So, I think that this test is probably inadequate for what we think it is doing, and I think if we look at some of the studies showing that even when people get treated with bisphosphonates, which are, you know, decreasing osteoelastic ability, so you are getting a denser bone, they are still getting fractures. So, in a little bit... in a way, it is kind of a red herring, in my mind. So, I'm... I'm not certain that the money spent on this test is actually well spent and we should probably take a step back and look at other things that really determine fracture risk for people, and that is very multifactorial. So, that is where I am at.

Craig Blackmore: Anybody else want to comment?

Chris Standaert: Yeah, I mean, I agree. It is difficult, and I think we weren't... we aren't actually looking at DEXA compared to other things. So, we aren't looking at DEXA compared to FRAX. We aren't given this report in the... the way things were structured wasn't structured in a way to say what is a relative benefit of DEXA versus FRAX versus fracture index versus whatever? We don't have that data. We have this, but that wasn't part of the study. That wasn't the intent of the report. So, we are looking at DEXA in isolation and trying... and I'm trying to, in my head, sort through how it... it is changing outcomes on fracture and even fractures are busy. You're getting a fall risk and all this stuff, and are you better off with fall prevention things? You are better off with bone mineral density things? Are you better off with making people stronger so they don't fall so easily and bounce? I mean that whole thing tumbles in my head as to what you're really trying to do, but it looks like it is sort of universally accepted by payers and by the Preventive Taskforce and by CMS, but it is difficult to see, almost Kevin's question, how did this get to be the thing that everybody is using as a way to base this, and there is always some, almost, I don't know, false

security in a number because you think the number means something, but the number doesn't mean what you think it means. Then it is... it is... I mean I deal with back pain. So, I look at hemorrhoids all day long—hemorrhoids and back pain are really difficult, right? Just because you can see it doesn't mean that that is a problem or that it is a thing and... and you... and many bad things happen to people because of what their MRI looks like that don't help them, so.

Kevin Walsh: Can I just get a clarification? When I read key question one, it doesn't assume that we are talking about DEXA. It... it says screening. All the subsequent questions are im-... imply that we are looking at DEXA. So, just for the sake of this discussion, should I shut up about FRAX and just accept that we are talking about DEXA here and that it is a given?

Teresa Rogstad: Could I comment on that?

Craig Blackmore: Yeah.

Teresa Rogstad: DEXA is for assessing low bone mass, and FRAX is predicting fracture. So, they... they serve two different purposes.

Craig Blackmore: I thought you said DEXA would... DEXA wasn't... DEXA is stratified to predict fracture... fracture risk.

Teresa Rogstad: Well, it has been... it has been found to be a good... that bone mineral density has been found to be a predictor of fracture risk, but DEXA scanning is performed to determine low bone mass, and the best... the best prediction of fracture risk, at that point then, is to combine that information with other risk factors.

Craig Blackmore: So, so...

Teresa Rogstad: But, but... with that being said, it would have been nice if we had found studies that compared fracture prediction...

Richard Phillips: Mm-hmm.

Teresa Rogstad: ...based on everything minus BMD and fracture prediction with BMD added in, and we... there doesn't seem to be anything.

Craig Blackmore: So, in answer to Kevin's question, the key questions are directed at technologies to assess bone mineral density, which doesn't include FRAX, and of the ones you looked at, the only one there where there was any real information was DEXA. So, we are looking at DEXA.

Kevin Walsh: Thank you.

Teresa Rogstad: Well... well... actually the PICO statement restricted the intervention to DEXA scanning, just because it is standard.

Craig Blackmore: OK.

- Teresa Rogstad: And that... and, you know, the definitions of osteoporosis are based on DEXA scores.
- Kevin Walsh: OK.
- Craig Blackmore: So, we are looking at DEXA.
- Kevin Walsh: Right. I cannot go up river.
- Craig Blackmore: Alright, other thoughts?
- Marie Brown: I think at this point, DEXA screening is built into EPIC as one of the... I know... but, it is one of the things... it's one of the quality measures.
- Craig Blackmore: It is... it is an external quality measure.
- Kevin Walsh: It doesn't matter.
- Marie Brown: I mean, I know. I know. I am just contributing the context of which this decision is.
- Kevin Walsh: Can... I want to ask a question of our clinical expert. I am just trying to think of how this stuff is used. So, say you have a patient who has a FRAX score that would indicate they are at high risk for fracture but you either don't have a DEXA scan or you have an equivocal DEXA scan, how are you going to counsel that patient?
- Christopher Shurhart: So, you are speaking about FRAX with a bone mineral density test versus without a bone density?
- Kevin Walsh: No. I am saying you... you have a patient who has a FRAX and either you have... don't have a bone density scan yet, or you have one that is equivocal.
- Christopher Shurhart: Alright, I am still... I want to make sure I'm hearing you correctly. The patient has a FRAX or a fracture?
- Kevin Walsh: Has a FRAX.
- Christopher Shurhart: FRAX.
- Kevin Walsh: A FRAX score...
- Christopher Shurhart: OK.
- Kevin Walsh: ...that would indicate they are at increased risk for fracture...
- Christopher Shurhart: OK.

Kevin Walsh: ...and they either have... don't... you either don't have a... so the two situations, one you don't have a, a BMD...

Christopher Shurhart: Yes.

Kevin Walsh: ...or two, you have a BMD that is equivocal.

Christopher Shurhart: Yes.

Kevin Walsh: What, what happens in that clinical scenario?

Christopher Shurhart: Well, we will talk about here in the United States, because FRAX really only gives us numbers for fracture risks, doesn't tell us about treatment thresholds. That is actually specific for particular circumstances around the world and, in fact, the WHO is very... stresses that. Each country sort of developed its treatment thresholds, and the U.S. has theirs. So, you know, the... the first disclosure is, I am a... I do osteoporosis every day and I see bone densities every day. So, I rarely operate without bone density. If... but I can give you a corollary, and the corollary is, if I have a patient who comes in with multiple risk factors for fracture and has had a compression fracture of the spine, if you told me that I could not have a bone density test, I would say, OK, I will treat this patient. That is a high-risk patient. That's a little on the edge of your question. I personally if... if I didn't have access to a DEXA machine and I used FRAX with BMI to calculate fracture risk, I would be happy with that, and there are many places around the world where that happens, since the access to DEXA here is quite substantial, and many places around the world there isn't that access. Does that help?

Kevin Walsh: Yeah, thank you.

Chris Standaert: But if you had that patient and you had, you know, a high risk for fracture on the FRAX and actually had a fracture...

Christopher Shurhart: Yes.

Chris Standaert: ...right, and we are too... I think in here someone said if they have a fracture they... they meet the diagnosis already. You don't even need a...

Christopher Shurhart: Right, that is called a...

Chris Standaert: ...a DEXA.

Christopher Shurhart: ...clinical osteoporosis, right.

Chris Standaert: When I see compression fractures, they all get DEXAs. In fact, they get lots of DEXAs.

Christopher Shurhart: Right.

Chris Standaert: They get them all the time.

- Christopher Shurhart: Right.
- Chris Standaert: Every year and... but they already had the diagnosis, because it broke. You don't even need the DEXA.
- Christopher Shurhart: Right...
- Chris Standaert: So, if you have this person who has a high score on a... a... sort of a, you know, a FRAX indicative of a high risk of fracture with a known fracture, and you get a DEXA and the DEXA is, you know, normal...
- Christopher Shurhart: Yes.
- Chris Standaert: ...do you still... you cannot just... you... you have to treat them.
- Christopher Shurhart: No. In that case, if the DEXA was stone cold normal, I would be thinking twice or three times about that I would be...
- Chris Standaert: About treating them?
- Christopher Shurhart: ...yes, right, if, if every single site...
- Chris Standaert: But if you know they already broke.
- Christopher Shurhart: ...that I measured was normal, because sometimes bones break, and it's not because of an abnormality in bone strength, right? So, distribution of loads that will break bones, sometimes normal bones break under abnormal loads.
- Kevin Walsh: But that, I mean, that's..., that's probably an unusual situation.
- Chris Standaert: [inaudible]
- Kevin Walsh: That isn't considered normal. I am... I am thinking more along the lines where they have an equivocal, like... like a T-score of -1. Yeah, something like that.
- Christopher Shurhart: That would be a risk-factor based model, right, so it would be the accumulation of risk factors for someone with osteopenia and a fracture, but generally, someone who had a T-score between -1 and -2.49, so below the osteoporosis threshold, but not normal, and had a compression fracture with even one risk factor for fracture, smoking or steroids, I would treating that patient.
- Kevin Walsh: What about the same scenario without a fracture?
- Christopher Shurhart: I... I would be looking for an underlying, correctable cause of osteoporosis more deeply before I went and treated that patient. I would look for some other metabolic problem that is not osteoporosis causing decreased bone strength.
- Richard Phillips: I have a question, just to clarify. I am... I am having a little bit of a problem with this. So, it gets back to what Chris brought up about the sensitivity, specificity of

a screening test and how this thing really doesn't fit in with this sort of... the model just doesn't fit in with it and I, you know, it seems to me that you can identify 90% of the patients. I may be wrong. I'm not a... I don't practice family practice, and I don't see these patients, but it seems to me you are going to see a lot of these patients by identifying their high risks right up front, and it makes me wonder why is it even necessary to do the study, screening study when you can probably predict 90% of the time and, you know, if we are trying to make a recommendation for doing a screening study, I would like to think that it is going to have some sensitivity, specificity tied to it, and I wonder if you could comment upon that, as to whether it is really... do... how necessary do you find it in the identification of these patients for treatment?

Craig Blackmore: So, maybe I will... maybe I will jump in a little, because there has been a lot of talk about sensitivity and specificity. So, accuracy and sensitivity and specificity are based on a binary outcome, the presence or absence of a disease and how good your test is at detecting that, and unfortunately in this case, we aren't dealing with the detection of a disease. We are dealing with identifying the probability of an event occurring in the future. So, a positive DEXA scan doesn't, positive meaning -2.5 or whatever it is, doesn't mean that you have a fracture and it doesn't mean you will develop a fracture. It means you are at a somewhat higher risk of developing a fracture. So, sensitivity and specificity for a current event or an event in a short timeframe would be abysmal, because the test is only going to say your risk is 15% or something. So, sensitivity and specificity, you can sort of force it into this construct, but really what you need to understand is how good it is at stratifying. How good... if it says the risk is 20%, what are the error bars on that risk in a given population, which I think we do have. So, we, you know, we have information about the diagnostic ability of the scale or of the DEXA, even if it isn't in the format we are used to looking at and... and... and the area under the curves that are given, again, are not necessarily that clinically relevant because it's not a binary outcome. Maybe I will leave it at that.

Christopher Shurhart: So, you're really asking how it adds additional actionable information. Is that essentially the question?

Richard Phillips: How... how it is critical, you know, and what percent... and maybe this isn't a fair thing to say, but do you... do you really need the test in order to basically treat patients? It seems to me you are going to identify the high-risk patients fairly easily.

Christopher Shurhart: Right. I think there's really... I like to think of two out... outcomes for treatment, right, and the first and gold standard is fracture prevention, and... and the second is conservation of bone mass. We all lose bone over time, and the less bone you have, this is, this is kind of, I think getting to some of that gradient of risk things that... that are more intrinsic to DEXA measurement than sensitivity and specificity, the lower the bone mass, the higher the risk for fracture, and it is true that most people with osteoporosis over a short period of time do not have fractures. The lifetime probability, you know, at age 50 with a T-score of -2.5 is 35 to 40%. So, only half of patients have fractures. That means maybe more than half don't. So, we are trying to reduce that probability and not

eliminate the risk for fractures. Using the test for me, as a... as a practitioner, helps me discriminate... there is a difference in my mind between a set of risk factors for a patient and a T-score of -1.1, and a set of risk... same set of risk factors for the same patient and a T-score of -2.4, and there is a gradient of risk there. There is some difference in risk relationship between those two [inaudible].

Richard Phillips: Well that makes my point is that using this as a screening test doesn't seem to make sense. In other words, you're going to make the... see the patient first, then make the decision to put... give the test rather than use it as a screening test because of a patient's age. Does that make sense? Am I... maybe I am wrong.

Teresa Rogstad: Well, it... it would still be a screening test because you are... you can screen in a high-risk patient or population. It is considered screening test, because you don't have signs or symptoms of osteoporosis. If a fracture had occurred, then it isn't a screening test, but if no fracture has occurred, it is still a screening test, even if there are risk factors.

Richard Phillips: But as it is set up right now, the screening test is for every woman over the age of 65. That's the recommendation, and that seems to me to be pretty liberal for but maybe... maybe I am wrong. Don't get me wrong. I may be wrong about that, but it seems to me that it is being used as a screening test sort of generically.

Teresa Rogstad: Well, then in that case the risk factor would be age. So, it is still a high-risk population, or could be considered such. I... I also found that sort of the study that seems to be cited a lot regarding the predictability of bone mineral density and what that study found was that spine osteoporosis has a... is associated with a relative risk of 2.3 for a spine fracture and osteoporosis in the hip is associated with a relative risk of 2.6 for hip fracture. So, that gives you some sense of how accurate a predictor it is.

Richard Phillips: Alright.

Kevin Walsh: Can I ask kind of the reverse question? So say, you... we know that age is a risk... is a risk factor, but say you have a patient who is 65 or 60... 60 whatever who has, with the exception of age has no other risk factors, um, and has a... and then... I guess what I am getting at is... so how... how effective is the FRAX tool at discriminating patients who are at higher risk versus lower? So, what we have heard is that for patients 65 and over, in general, there is approximately a 10% risk of them having a fracture in the next 10 years is that... is that correct?

Christopher Shurhart: Correct.

Kevin Walsh: So, and... and what we are talking about is using the DEXA scan to try and stratify patients as to whether they are more likely to be... to have the fracture versus less likely to have the fracture, and so... I guess what I am curious about is, how do you use the FRAX in that situation? Is it... is it useless if the patient has no other risk factors and the DEXA is the only thing you have to go on, or...

or is the DEXA only offering you a marginal benefit over the FRAX for a 65-year-old without any obvious risk factors?

Christopher Shurhart: So, the DEXA scan, at age 65 let's say, verse... with FRAX versus without, and... and offering benefit. I think if you went to the FRAX tool, and I think Teri just punched it up, you would see differences in predicted risk. That would depend a bit on... so... so FRAX without bone density is driven by BMI. BMI is the surrogate for BMD, and it works very well for patients who have, as a surrogate, for patients who have normal or high BMI. When you start to get to lower BMIs, the ability of FRAX to predict risk is... is aided by the addition of BMD. So, thinner people, particularly as you get older, the fracture risk prediction is more accurate. Will, I'm not going to... I don't want to use the incorrect term, there is better fracture risk discrimination in patients who have BMI... BMD added to their FRAX calculation when they are thin versus it doesn't matter as much when they are of normal or high BMI. So, it is a bit of a complicated answer to the question, but there are a number of... lots of cohorts have been reanalyzed with FRAX and show the same propensity to increase fracture risk prediction in patients with low BMI.

Kevin Walsh: OK, and that is a really interesting point that I don't think we heard anything about up to just now, and I am wondering, Teri, can you make any comment about discriminating those two sub... sub-cohorts, those with normal or... or above average BMI versus those of low BMI?

Teresa Rogstad: No. I can't. I am afraid we didn't look at that.

Craig Blackmore: Can I ask, Christine, can I ask you to put up slide #10 from the agency director's presentation? Maybe we can all turn to it, and I... I am going to make sure I understand what this table is showing me but it... it seems to indicate, slide 10, yeah. That is it. This seems to indicate the ability of the BMD measurement to differentiate among risk in women of different ages both with and without risk factors.

Teresa Rogstad: That... that is... I did that slide, and this is for a weight of... I want to say 70 kilos and I think 5'4" in a female. So, I didn't use a... a lower BMI for this, but... but I put that... those parameters in, age 65, for the different ages using the BMD and then not using the BMD for each of those T-scores. So, that is what that... that shows.

Craig Blackmore: So it maybe gives a little bit of a visual idea of the ability of the BMI to contribute, you know, versus... zero versus one risk factor from the FRAX and how the BMI fits in.

Teresa Rogstad: BMD.

Craig Blackmore: BMD, sorry, BMD.

Kevin Walsh: Yeah, this... this slide underwhelms me.

Christopher Shurhart: Just pointing out... trying to answer the question.

- Kevin Walsh: Well, it is because it is expressed in absolute risk instead of relative risk. So, right away you have taken away some of the power of obfuscation.
- Chris Standaert: This is a... this is a modeling thing. This isn't... this is modeled off of data they have. This isn't actual data. This is a modeling.
- Teresa Rogstad: This is modeling using a tool.
- Chris Standaert: Computer deal, and then you get into question of how often somebody with no risk factors whatsoever has a T-score of less than 2.5, which is probably not very often that they have zero risk factors, I would assume. I don't know.
- Christopher Shurhart: The risk factors can relate to bone density or bone quantity.
- Chris Standaert: Mm-hmm.
- Christopher Shurhart; But many risk factors relate to bone quality, specifically things like microarchitecture, bone mineral metabolism. Bone density compresses a lot of information...
- Chris Standaert: Mm-hmm.
- Christopher Shurhart: ...so to speak about bone into a two-dimensional assessment and it is very clear that factors of bone quality that are not... that are somehow either not obtained or filtered out in that compression...
- Chris Standaert: Mm-hmm.
- Christopher Shurhart: ...of bone density impact risk, and those are quality... those can be quality factors that contribute to strength nonetheless.
- Teresa Rogstad: To respond to your point, Kevin, about the... the sort of obfuscation... it is a hard word to say, of using the risks this way, I mean, part of the reason I chose this was because if you look at the absolute risk based on these various conditions and ages, I was struck by the fact that it is less than 10%, and so to me, that discussion with the patient is a little bit different, it is more of a shared decision-making discussion given that low absolute risk. So, to me, I... I purposely did it that way, because I thought we are talking about a 10% risk, at most, over a 10-year span and... and that, to me, warrants a pretty careful discussion with my patient about whether or not they want to take a bisphosphonate every day, set up for a half an hour, and then have a better than not chance of having GI distress. So... so I purposely put it that way for just to reflect that piece.
- Chris Standaert: I just have one question for the... the tracking of these and... and DEXAs over time, because I have a lot of patients who get a DEXA and they are treated for their osteoporosis or osteopenia associated with a fracture or without, and they are very anxious about whether or not that number will change when they get their DEXA next year, and they get it the next year, and they get it the next year,

and it changes 2%, 5%, 3%, 7%, 8%, and they are happy or they are despondent when they get their DEXA, and what I am getting from this is... that that doesn't really help anybody at all. It is a risk stratification tool, and it, again the treatment you are giving them isn't meant to necessarily alter the measurements on the DEXA. It's meant to alter their risk profile over time. Frankly, I don't think they understand that, and I don't think most of the people who are treating them are really putting it in those words if they understand it, but that is what is happening and people, again, they live on the number and, and it creates a lot of anxiety out there, I think. Do you find that in your practice?

Christopher Shurhart: Yes. Yes. We are, you know, people are... like lots of, I mean, we are trained to do this, right? So, as physicians we are trained to do this. We want to... we want... we want to make sure we are doing the best thing for our patients and sometimes the thing we are doing isn't necessarily the best thing. So, the analogy I use with patients all the time is blood pressure, right? So, you come in to your doctor's office after you have started on your blood pressure medication for a month and your systolic blood pressure has gone down 13 points, and everybody is happy and the discriminatory ability of that to predict your reduced risk for stroke or kidney failure is not so much in that number, it is in the fact that you are taking the medication the way you are supposed to. So, we know this about bone density measurement, too, and... and now we are sort of talking about serial monitoring versus screening for patients who are on treatment. It is a little different story but the key thing for me, as a clinician, and maybe I am a little different, but is getting patients to understand that taking the treatment the right way, at least based on the results from the clinical trials, is what is going to reduce your risk for fracture, and yes, we are happy when your bone density stabilizes or goes up, which happens in probably 85% of cases. We aren't as happy when bone density declines, but ultimately we are trying to treat you so that nothing happens to you. You will not feel better. You will not look better. You will not have a fracture, or at least you will have a lower probability of a fracture.

Craig Blackmore: OK. So, I'm still looking for a framework to address this problem but I think what we're hearing, and I want to find my key questions and make sure I'm on target is, where are the key, there they are. So, there's, yeah, so we are looking at all of these. So, the... the first issue... I'm going to just sort of lay these out and then we can talk about how to address it. The first issue is among sort of asymptomatic individuals do we reimburse for screening and with what frequency and in what sort of age groups, etc.? That's the first issue. The second issue is, among patients who have a fracture, so patients who are symptomatic from their osteoporosis or at least have clinical disease from their osteo... I won't say clinical disease. Patients who have a fracture, we'll leave it at that... what... what are we going to do with that group? And then a third question is around patients who have already been diagnosed and presumably are getting treatment, what would be the sort of follow-up interval, if any, for monitoring of serial testing as it list... as it's listed here? So, I think there's at least three distinct questions, and there may be that... that first question about screening includes both who and with what follow-up interval. So that's kind of a two-part. So, I think there's those three groups. Is that... does that resonate?

- Kevin Walsh: I... you... you made a distinction between monitoring people with fractures and not and people without fractures.
- Craig Blackmore: So, there's... there's... if... if you think about it... if you think about screening, so supposing we say screening...
- Kevin Walsh: No. I'm talking about monitoring after.
- Craig Blackmore; Right.
- Kevin Walsh: So, I'm further downstream than that.
- Craig Blackmore: Oh, so there's, there's two parts...
- Kevin Walsh: Because you said...
- Craig Blackmore: ...to monitoring. Right.
- Kevin Walsh: ...you... you were talking about monitoring people with fractures as one group and then monitoring people without fractures as another group.
- Craig Blackmore: So, that might... that might be...
- Kevin Walsh: I don't think that's a real distinction. It might or might not. I mean, it's up to us.
- Craig Blackmore: OK. There... there's screening who and with, at what interval. There's imaging in patients who... who have a fracture. So, they meet the definition for having osteoporosis. Is there any incremental value?
- Kevin Walsh: Osteoporosis is based on your T-score, not a fracture.
- Craig Blackmore: Or in the presence of a fracture.
- Kevin Walsh: Right, but most of the information that we looked at was based on your T-score, not the presence of a fracture.
- Craig Blackmore: OK, so we can talk about that, but in terms of groups, one group is screening who and at what interval. The second group is do we fund DEXAs on individuals who already have osteoporosis defined by the presence of a fracture? And the third question is what... what is the, you know, what are we... either cover or not cover for patients who already have diagnosis of osteoporosis from whatever source? And do we allow for follow-up, reimburse for follow-up DEXAs in patients?
- Kevin Walsh: Well, I would broaden it to look at... at rescreening in general.
- Craig Blackmore: So, that's the first, first question is, do we allow screening?
- Kevin Walsh: Rescreening.

- Craig Blackmore: ... and if so...
- Kevin Walsh: Rescreening.
- Craig Blackmore: ...yes, and at what interval? So, that's rescreening.
- Kevin Walsh: OK. You're... you're bunching screening and rescreening together as one question.
- Craig Blackmore: Yeah, screening means you... you do a test and then usually in a screening program you repeat that test at some defined interval. So, we would talk about what that would look like. Maybe it would be one only. Maybe it would be a second one at some number of years depending on all these factors, but they're... you're still screening. You're still doing the DEXA scan on people who are asymptomatic to identify their risk, and then a second group is people who meet the definition of osteoporosis because of a fracture, what would be the appropriate use of DEXA in that group? And the third group is people who have already... were already treated, in essence, for osteoporosis diagnosed by either a fracture or... or their T-score, if they're being treated, what would be the appropriate follow-up interval to basically assess success of treatment, if any?
- Chris Standaert: I guess I have one other question, and I guess it's the word screening. I don't know if we're screening or not screening, because you look at, when I... I was just looking through some of the guidelines on things, people who are in special populations, and so if you have somebody who is a male gets put on glucocorticoids or a male gets put on hormone suppression for prostate cancer, and you're watching their bone density, is it actually screening or is that, that's not really...
- Craig Blackmore: It's not screening, but we're going to look at it anyway.
- Chris Standaert: So, we're going to... but we're going to set them as a different pop... this is a special population in people, then, who have some medically-induced hormonal event that has made them at risk for progressive bone...
- Craig Blackmore: So when...
- Chris Standaert: ...mineral density loss and, and you're almost doing it not so much to find their risk fracture to treat. You're trying to sort of see what's happening... how badly is their bone reacting to what you're giving them, I would assume? That's why you're doing it in those people?
- Craig Blackmore: You're... you're monitoring the complications of their treatment, but... but I think we can consider them with the screening group. So, screening will be stratified based on various things. Maybe it's age. Maybe it's risk factors. Maybe it's gender. Maybe it's, you know, drugs you're taking for other reasons or... or whatever, and then of course it isn't strictly screening, but we can be... we can use the term I think.

- Richard Phillips: I have a little bit of a nonexecutor question. For clarification, you could answer this Craig, what's a fragility fracture as opposed to standard fracture? Is that a special kind of radiographic fracture?
- Craig Blackmore: Well, how do you define fragility fracture?
- Christopher Shurhart: So, fragility fractures, really there are three characteristics of a fragility fracture. Fragility fractures predict future fragility fractures. That's the first notion, that fractures beget fractures, and there are only certain sites in the body where that... where there is a... a gradient of risk for a next fracture where that holds and... and the general agreement, like for FRAX, FRAX defines fragility fractures, for instance, as part of the... part of the modeling as a low energy fracture. So, that is the second part of the definition, a fall from a standing height or less, sometimes people will extend that a little bit. So, fall from a standing height or less or the equivalent energy thereof that creates a fracture that increases the risk of another similar fracture down the road and generally has increasing incidents with age. So, those are the three characteristics.
- Richard Phillips: So, it, it's always radiographically evident?
- Christopher Shurhart: Well, if...
- Richard Phillips: Is that fair to say?
- Christopher Shurhart: Well, ultimately, that would be the adjudication of the fracture. So, we can define... there are different ways to, for instance, to define spinal fragility fractures. There are radiographic ways to do that and then there are clinical ways to do that so people can have asymptomatic, in fact, most spinal fragility fractures are asymptomatic. They aren't acute fractures. They are chronic fractures. The bone literally compresses over time. That is about 60% of spinal fragility fractures. The other 40% are symptomatic, and then the rest of the fractures, the typical sites are hip, and there is a number of locations in the hip but we'll say hip, proximal humerus, distal radius, pelvis, sometimes rib, but those are generally the five areas along with spine.
- Richard Phillips: So, would that be part of our risk factor thing that we'll be talking about, or... in other words, just like the prostate cancer patients being treated with a...
- Chris Standaert: Doesn't the presence of a fragility fracture meet... make the diagnosis of osteoporosis?
- Christopher Shurhart: The presence, well... so the World Health Organization and the National Osteoporosis Foundation, for instance, say the presence of a vertebral or hip fragility fracture.
- Chris Standaert: Not wrist or humerus?
- Christopher Shurhart: They don't go that...
- Chris Standaert: Or sacrum.

- Chris Standaert: ...they don't go that far. I would, particularly for just a radius fracture and proximal...
- Chris Standaert: Right.
- Christopher Shurhart: ...humerus fracture, sometimes for pelvis fracture, but that's what NOF and [inaudible] state.
- Chris Standaert: I guess the fracture alone is what's making the diagnosis.
- Christopher Shurhart: Correct, that's... it's... it's a sign that skeletal strength has been compromised and that future fracture risk is increased.
- Craig Blackmore: OK. So, I think, again, I'm just trying to narrow things down so we can make some progress and... and I think, tell me if you disagree, but I think the... the best way to do this is to start with what we're calling screening, which is basically the use of DEXA in an asymptomatic population in order to fine-tune an estimate of risk so that they can be treated as appropriately for osteoporosis, and so the question for us is, in which, if any, populations or subpopulations should we fund this and if so, at what interval would we fund additional screening? The U.S. Preventive Service Taskforce has its recommendations. There are society recommendations. There's data for what it's worth. So, what do we think?
- Richard Phillips: You know, as a starting point, I really didn't have any problems with the... the recommendations by the state as to what should be covered and what shouldn't be covered. I think the... I can't remember which slide it was where it had all the list of from AETNA, CNS, there's a bunch of high-risk exceptions in there that might... we might want to consider but as a starting point, I would not have a problem with at least starting where the state was.
- Craig Blackmore: OK. If I could ask Christine, maybe we could get those up there so we can, they're...
- Teresa Rogstad: They have a cover with conditions.
- Craig Blackmore: So, I mean, again, I'm... I'm assuming, and tell me if I'm wrong, I'm assuming there is not a general feeling among the committee that we should have a complete cover, anybody who wants one, right?
- Group: Right.
- Craig Blackmore: So, that means we are either dealing with we never fund screening DEXA or we cover it with conditions, and so it's a place where we often are, and it becomes a matter of trying to figure out what conditions, if we go that way, what conditions would be most appropriate. OK, so I think probably we start with women, since that seems to be the... well we'll start with women. So, the proposal that we're starting with is... we would cover DEXA for women equal to age 65 or... so this would be the initial screen.

- Michael Souter: Craig?
- Craig Blackmore: Yes.
- Michael Souter: Can I just ask something?
- Craig Blackmore: Yes.
- Michael Souter: Just as you brought up that point there, I mean, should we settle the question is there anyone who thinks that we should get rid of, you know, not fund DEXA altogether? You mentioned that. We are either in a position that we're not going to do it, or we're going to cover it with conditions.
- Craig Blackmore: We can do that.
- Michael Souter: Before we hone in the conditions, should we just settle the question of whether or not we're...
- Craig Blackmore: Either one would be fine, I think. Is there, I mean, informal show of hands, is there a sentiment that we should never allow... we should never... we should not cover DEXA under any circumstances? OK, so we haven't voted. So, you can still decide that later, and you can still decide to cover without conditions later, but we're... we're at least tentatively coalescing in that middle ground.
- OK, so... so thoughts on initial if we cover with conditions having one condition be that initial screening occurs at or equal, in women, at age 65 or in younger women with risk factors suggesting a 10-year fracture risk equivalent to that of a woman aged 65, which would be... we are told, 9.3%. Can I get some feedback on that as a starting point?
- Richard Phillips: I personally am happy with that. I might stipulate that it use the FRAX tool, but I... I don't know if that's reasonable or not, but...
- Michelle Simon: Yeah, so that would be the question, how are we calculating that?
- Richard Phillips: Yeah. Pardon?
- Michelle Simon: So that is the question, how are we calculating the 10-year fracture risk?
- Carson Odegard: 9.3%.
- Richard Phillips: Yeah.
- Michelle Simon: 9.3%. I mean, any estimation...
- Richard Phillips: I think we almost...
- Carson Odegard: It's off the FRAX.

- Richard Phillips: ...well, I... I'd say yes personally but I, you know, there's a thousand different ways to do it.
- Craig Blackmore: I mean, do you want to say a risk calculated by, you know, accepted instrument or tool that somebody didn't just guesstimate? Do we want to say it has to be the FRAX? I think it... I think it's probably... does everybody use the FRAX, I mean?
- Christopher Shurhart: The answer is no.
- Craig Blackmore: No.
- Christopher Shurhart: There are a number of other tools that can be used. FRAX is probably the most robust and FRAX... the two other major tools that are used potentially in the United States are a thing called the Garvin Nomogram and another tool called the Q-Fracture Model. The Garvin Nomogram and the Q-Fracture model have some vagaries that make them... speaking about, like, area under the curve for instance, make them a little less predictive, just... significantly but... but a little less predictive of fracture risk than FRAX. Mostly, FRAX uses competing mortality. In other words, the risk of dying lowers your risk of fracture.
- Craig Blackmore: Yeah.
- Christopher Shurhart: And as you get older, that becomes significant, and so what happens if you look at graphs of fracture risk in FRAX, as you get older, your fracture risk starts to go down, because your 10-year probability of a fracture goes down as your risk for dying from something else goes up, and so FRAX is probably now the most widely used of the tools accessible online, on a handheld device, on paper, and I would say it's probably the most widely used.
- Kevin Walsh: And it's free.
- Christopher Shurhart: Uh, it's \$5.99 for the app.
- Craig Blackmore: For the app.
- Christopher Shurhart: For the app, yeah. No, it's...
- Teresa Rogstad: You can go online.
- Christopher Shurhart: ...free online.
- Craig Blackmore: OK, well I think... I mean... I guess looking at this, if we're saying a 10-year fracture risk of 9.3% and that 9.3% comes from the FRAX, then it's appropriate to say you need to use the FRAX and if, you know, if we wanted to do a different rule for every instrument that's out there, we could but the FRAX is simple enough that anybody should be able, even if they like another tool, they should still be able to say, alright, you're a, you know, 64-year-old woman with the following risk factors, and the FRAX would enable them to meet this requirement.

- Kevin Walsh: You could just say with, with equivalent risk of a 65-year-old.
- Craig Blackmore: You could say that, calculated by a validated tool.
- Carson Odegard: So, in clinical practice you are assuming that if you're 65... if you're a 65-year-old woman then you have a certain risk factor that's built into that age and that... there needs to be... or the clinical decision making and to have a DEXA scan isn't based on any other testing other than just the age, is that... is that what we're saying?
- Kevin Walsh: Yes.
- Carson Odegard: OK.
- Kevin Walsh: That's what we're saying.
- Chris Standaert: And we're basing this on the current study? I mean, our evidence for stating this is? We're saying this because the director said this or we're saying this because the Preventive Taskforce said this? We're saying this because of the current study? We're saying this because...
- Craig Blackmore: Well, this is the U.S. Preventive Services Taskforce recommendation, which the agency has put here to give us a starting point, but we are not... I mean, we are not doing it because the agency recommended it. We're doing it because...
- Chris Standaert: I'm just making sure we have our, our...
- Craig Blackmore: The U.S. Preventive Services Taskforce...
- Chris Standaert: ...our basis for the...
- Craig Blackmore: ...gave it to us as an anchoring point, and we don't have a reason to go differently.
- Kevin Walsh: Can I ask one more question of our clinical expert?
- Craig Blackmore: We can.
- Chris Standaert: But actually that, OK.
- Kevin Walsh: Maybe this has been covered, but just, just to see how that would actually work. So, you have a patient who's 65 who gets screened because they're 65, and they come back with an elevated T-score of, or a decrease, I don't know how you state it, but a -2.5. Is that a person that you would necessarily recommend treatment for?
- Christopher Shurhart: Generally, yes.
- Kevin Walsh: OK, and if they're, and if they're -1.0?

- Christopher Shurhart: No.
- Teresa Rogstad: No.
- Kevin Walsh: OK. So, that... so this is the... the DEXA scan in this patient is the one that's going to differentiate whether you will treat or not treat?
- Christopher Shurhart: That... that would be an important factor, yes.
- Kevin Walsh: An important factor?
- Christopher Shurhart: Well, you, so there are a number... you said, I... I think you said 65. You didn't specify that we had any other risk factors available, correct?
- Kevin Walsh: Got it.
- Christopher Shurhart: OK. So, yes, it would be the DEXA scan in that circumstance that would make the difference.
- Kevin Walsh: OK, but if they had risk factors that would weigh into the equation?
- Christopher Shurhart: Yes.
- Kevin Walsh: But, but in the absence of other risk factors, the DEXA scan alone will, will induce you to recommend treatment?
- Christopher Shurhart: 65-year-old, T-score -1.0, we'll treat.
- Kevin Walsh: Thank you.
- Craig Blackmore: Alright. So, I think the suggestion has been made that we pull up the U.S. Preventive Services Taskforce 2010 recommendations, which are on Teri's slide 12, as a more rigorous starting point.
- Chris Standaert: The language for that doesn't say anything about 9-point. It says a 10-year fracture risk greater than or equal to of a 65-year-old white woman.
- Christopher Shurhart: I think, because it's FRAX, it'd be in the body of [inaudible].
- Chris Standaert: What I want to know, there's an asterisk. I don't know if that asterisk is from the taskforce or from the person putting the slide together.
- Craig Blackmore: Yeah.
- Christopher Shurhart: What's that?
- Craig Blackmore: I mean, I... I'm happy saying it has to be FRAX, or I'm happy saying it's risk, but if... it's probably worth specifying that it has to be on some validated instrument that it's not just gestalt, although I don't think it would be.

- Chris Standaert: Is it fair to say FRAX or equivalent validated instrument?
- Craig Blackmore: Fine with me.
- Chris Standaert: Or do we just leave it at FRAX?
- Craig Blackmore: OK. So, now we need Christine to give us a blank piece of paper and start writing it down. Oh, you're ahead of us. Look at this. This is good. A woman with... this glare is, equivalent 10-year fracture risk calculated by FRAX.
- Chris Standaert: Is greater than or equal to 65. Yeah, they have the equal sign, yeah.
- Craig Blackmore: Calculated by FRAX or other validated scoring tool. Alright, any thoughts on that? OK.
- Michelle Simon: So, my... I... I have a question. One, I was looking at some of the other agency guidelines in the... I guess this is page... slide 44. Yes, and it says screening in women, nine of the guidelines had age 65 or greater, and then three of the nine guidelines had all women during menopausal transition, and I was just looking at the FRAX tool, and I did not really see a place for menopausal transition in the FRAX tool. So, are we missing something here with the risk or not? I just want to.
- Marie Brown: It used to be what was recommended in clinical practice, but that was before...
- Michelle Simon: The FRAX tool.
- Marie Brown: ...before wide use of the FRAX.
- Christopher Shurhart: FRAX is validated for ages 40 to 90, so there are probably... you can predict risk for premenopausal women with FRAX, as well.
- Michelle Simon: And it's mostly the BMI that's doing that then, because I'm looking at the questions on the FRAX tool. I don't see anything in there.
- Christopher Shurhart: If you look... if you scroll down, I think it'll... it'll talk to you about the assumptions in the FRAX model, and it talks to you about validated for ages 40 to 90 somewhere. Is that, is that what you're trying to understand, where that 40 to 90 comes from, or?
- Michelle Simon: Well, I'm trying to figure out if, if somebody goes through menopause early...
- Christopher Shurhart: Yes.
- Michelle Simon: ...at 40 or something and...
- Christopher Shurhart: Yes.
- Michelle Simon: ...well away from 65...

- Christopher Shurhart: Yes.
- Michelle Simon: ...does that get calculated into this? I don't see it as on the questionnaire as one of the questions that's asked on FRAX.
- Christopher Shurhart: No, it would just be... it would just be age. There is no... there is no input for menopausal or non-menopausal.
- Michelle Simon: OK.
- Craig Blackmore: OK, what about men? Does the FRAX work for men?
- Teresa Rogstad: Over 70 [inaudible].
- Chris Standaert: We have no data on the FRAX on men in what we saw, correct.
- Craig Blackmore: So, may... maybe... maybe the clinical expert can help us understand the differences between men and women. That's kind of an interesting question.
- Christopher Shurhart: Their skeletons, or?
- Craig Blackmore: So, well, I'm wondering, I mean, if... if we're saying, you know, the threshold for women is 9.3%, 10-year risk. So, why wouldn't we use the same threshold for men and, and the answer might be because there are other differences between men and women that would make that not valid, and I'm...
- Christopher Shurhart: Right.
- Craig Blackmore: ...trying to understand that clinical context.
- Marie Brown: The risk is lower.
- Richard Phillips: Men don't have menopause.
- Craig Blackmore: Yeah, but if we're identifying men who are at the same risk, I mean, why... why would... if... if... why wouldn't we just say when men hit 9.3% we'll give them a DEXA based on the FRAX?
- Marie Brown: Well, we're saying just based on age, period, for women.
- Craig Blackmore: Or if you're younger but you're...
- Marie Brown: We wouldn't do that for men, because they have a lower risk.
- Richard Phillips: That's because we assume menopause, but with men...
- Craig Blackmore: But at some point, men are going...
- Christopher Shurhart: Right, so that's, that's...

Craig Blackmore: ...to be at 9.3%.

Christopher Shurhart: ...one of the critical factors is that... is that there is... there is predictable and generally substantial bone loss in women because of menopause, and that changes their risk profile, and that's, you know, between ages 40 and 50 for more than half of women in the United States, so that's one factor. It's... it's a different risk equation.

Richard Phillips: So it's an endo-, endocrine difference?

Christopher Shurhart: Partly, right.

Richard Phillips: Partly.

Christopher Shurhart: That... that's what... that's what drives an increase... a substantial increase in risk for fractures before and after the time period for women is, is menopause.

Marie Brown: So, the risk for fractures is less in men?

Christopher Shurhart: In men, yes... yes it is.

Craig Blackmore: Yeah.

Marie Brown: Clearly.

Christopher Shurhart: And, and, and so that's one reason. Another reason is men have bigger skeletons, larger bones than women do, and we could go into the physics of that if you like, but essentially bigger bones are stronger bones for the same amount of calcium per bone. The analogy I use with patients all the time is if I give you a piece of a coat hanger wire, twelve inches long, and it weighs something, and I ask you to bend it, you'll have no problem bending it. You can bend it until it breaks. If I take the same amount of material, and I turn it into a tube that has very thin walls but has a radius, and I give it to you and you try to break it, there's no way you can break it. It has the same mass, but it has much greater strength because of its cross-sectional moment of inertia. So, the bigger... men's bones in general are about 10% bigger than women's bones, and that confers about a 30% increased strength factor for men, independent of bone density. So, the risk relationships don't hold as much for men, and, and I'd caution you about extrapolating men and women from that risk value, because that's really based on a different set of... a different biochemical environment over time for women, and a different structural environment over time for women. There might be an equivalent risk value, right? There might... it might be 8.7% or 8.4% for men where it's equal to the risk at 65 or whatever other age you would ask for men, but I don't know of any data out there in that regard.

Craig Blackmore: But... but at some point in the FRAX, if it's valid for men, at some point it's going to spit out a risk of 9.3% for men.

Christopher Shurhart: Yes.

- Craig Blackmore: At some age.
- Christopher Shurhart: Yes.
- Craig Blackmore: So, why wouldn't I use that age as my screening cutoff for men? If I say that's appropriate for women, no matter how old you are, if your risk is 9.3% we're going to do screening, why wouldn't I go for men when your risk is 9.3% you're going to allow screening?
- Christopher Shurhart: So, the 9.3%...
- Craig Blackmore: Why are they different?
- Christopher Shurhart: ...the 9.3% value ties back to... that number is chosen because it represents the risk of the average 65-year-old woman.
- Craig Blackmore: Yeah.
- Christopher Shurhart: Right? So, the risk for the average 65-year-old woman and the risk for the average 65-year-old male...
- Craig Blackmore: Yeah, but I'm not talking about a 65-year-old man. I'm saying, at some point...
- Chris Standaert: When that man hits the risk of...
- Craig Blackmore: ...some age...
- Chris Standaert: ...a 65-year-old woman.
- Craig Blackmore: ...it may be at 78, maybe it's 90. I don't know what it is, but at some point, they are going to reach a threshold where...
- Chris Standaert: Right.
- Craig Blackmore: ...society, collectively, has decided it's OK to screen. Why can't I use that as my cutoff for men?
- Chris Standaert: So, the risk of that man is the same as the risk of a woman of 65 years old.
- Craig Blackmore: Yeah. So, I mean, why wouldn't I just take out the first two words after the or, or just say a person with equivalent 10-year fracture risk.
- Michael Souter: Mm-hmm, but given the available data...
- Craig Blackmore: I'm asking the question.
- Michael Souter: ...but, but given the available data, I suspect, I mean, I... I don't know... you can perhaps comment on this, but I suspect that they can have the confidence

intervals around those predictions for women and men relative to their gender are going to be, you know, considerably different in size.

Chris Standaert: Probably.

Michael Souter: You've got a kind of smaller confidence interval probably for women given the number and the frequency of the studies there. I imagine for men, that confidence interval, respective of the fact that you're crossing the same threshold of risk, is going to be so much greater.

Chris Standaert: And the real data we have... the trouble we have here, I mean, the Preventive Health Taskforce punted on men because they didn't have any data, and so, the only... the only data I see are from the same current study, and it's exactly what he just said that the confidence interval for men in that study is much broader. It's from 0.32 to 1.42 and they happened to pick 68 in the middle, but it's much broader than the confidence for women, which is 0.35 to 1.06.

Craig Blackmore: So, we're not allowed to punt.

Chris Standaert: Huh? I know we're not allowed to punt, but... but we also like to have some rational data-based decision for what we're doing, and we don't have that other than extrapolating out what you're saying that, that if you're going to pick something why don't you pick the same risk profile essentially?

Kevin Walsh: So, can I go back to the point that... that Seth made, which was, you asked the question if... without other risk factors, a T-score of greater than -2.5 in a woman without risks would push them into the treatment algorithm.

Seth Schwartz: He said -1.

Kevin Walsh: No. He wouldn't treat at -1 unless there were other risks.

Christopher Shurhart: -1... what he asked me was, at 65, T of -1, no other risk factors, would I treat. The answer is no.

Kevin Walsh: OK. The... so if you go back to Nelson, there was only one primary prevention trial for men, and it was using parathyroid hormone.

Craig Blackmore: Men using, yeah, men at high risk.

Kevin Walsh: So, there is basically no data that treating makes a difference. So, if there is no data that treating makes a difference, how do you logically decide to screen?

Craig Blackmore: Well, you... you can only do that if you think you can extrapolate from the data on women. I mean... that... that's...

Kevin Walsh: I don't have a pogo stick. I can't extrapolate that far.

Michelle Simon: So, I just played around with the FRAX tool just to see if I could come up with a number for you, 9.3, and I can't get beyond 6.6, and this is... I'm just putting an

age in, all the way from 75 to 90, like a 5'9" 180-pound male with no other risk factors and it's, the highest you get is 6.6.

Chris Standaert: So, you'd never make it.

Craig Blackmore: I mean, unless they're...

Michelle Simon: You'd never make it on FRAX.

Craig Blackmore: ...on a glucocorticoid...

Christopher Shurhart: Hold on a second. This refers to overall fracture risk. Are you looking at hip fracture risk or overall fracture risk there?

Michelle Simon: This is major osteoporotic. Hip fracture is much lower.

Christopher Shurhart: Right.

Michelle Simon: It's a below 2.9.

Christopher Shurhart: So, this is... this is with BMI not with BMD.

Michelle Simon: Correct.

Christopher Shurhart: Without...

Michelle Simon: Only BMD.

Christopher Shurhart: Right.

Michelle Simon: This is just BMD.

Christopher Shurhart: Right, and so it's... what the FRAX value is, is the value, right? So you... so you can't get to a 9... a 9.3 threshold.

Michelle Simon: Not for a male in this model.

Kevin Walsh: Can I, can I ask another question?

Christopher Shurhart: Right.

Kevin Walsh: Just to simplify this? Why are even specifying women greater than 65, because if they inherently have a value of 9.3, why don't we just say anyone with a FRAX value of greater than 9.3, you know, greater than or equal to 9.3?

Craig Blackmore: A FRAX value equivalent to that of a white average-risk 65-year-old. I mean, that's what we're saying.

Group: Yeah.

Christopher Shurhart: There is one other consideration on the back end. This is all about what do we do then, right? So, we're looking to treat to... to hopefully affect risk for fractures, and that is that men are differentially impacted, particularly from hip fractures compared to women.

Craig Blackmore: What do you mean... what do you mean by that?

Christopher Shurhart: Well, for instance, the one-year mortality post-hip fracture for men is higher than the one-year mortality for women by about a third. So, the overall...

Chris Standaert: Is that because they're older, but that I would have to assume...

Christopher Shurhart: No, that's because when... when they have a hip fracture, it's a sign of frailty.

Chris Standaert: Right, that's what I was going to say. That's a sign of general medical status. So, if a male falls and breaks his hip, he is likely to be much less well than men who fall and don't break their hips. That's a marker. That's not a cause and effect, and that may have nothing to do with bone density whatsoever their... their livelihood after that. I mean, that's an association sort of scenario.

Christopher Shurhart: Right, but in, but the...

Chris Standaert: So, I can't, yeah.

Christopher Shurhart: ...the practical way to that understanding is not the way that you have... you stated it. The practical way to the understanding for most practitioners, hopefully I'm not painting with too broad a brush, is through... through the measurement, the understanding of what's frail and not frail happens after the fracture, literally, not before the fracture. The fracture is the sentinel event for most practitioners.

Chris Standaert: But then you have... so in our standpoint, you then have somebody who meet... who has a... is in our special population. They have a... the fragility fracture or they have some other thing that somebody would be screening them to know what... whatever this... whatever their medical status is doing to their bone or do they have... they broke. Therefore, I'm really worried they have bad bone, may have some metabolic reason why they have bad bones, and they get the DEXA and wow, their bone is bad. I'm going to go chase this down hormonally now and see why they have a bad... why they have bad bone, but that's different from the screening population that we're talking about at the moment. So, the trouble is... we don't have any data on them. I mean... we don't...

Kevin Walsh: And that's why I propose that we don't cover men.

Michael Souter: Exactly.

Marie Brown: Right.

- Carson Odegard: Because 70 years old, what they're saying is a 70-year-old without any risk factors is equivalent to a 65-year-old.
- Chris Standaert: Yeah, so, so...
- Marie Brown: Which is not correct.
- Chris Standaert: ...but USPT didn't do that.
- Kevin Walsh: Right, that's what they're saying, but, but if you use the FRAX tool, it's not.
- Carson Odegard: It's not.
- Marie Brown: It's not.
- Chris Standaert: Yeah, we'd be saying you wouldn't use this in an asymptomatic male who isn't in a special population putting him at high risk for bad bone or with other markers that indicate they already have bad bone.
- Marie Brown: Right.
- Carson Odegard: Right.
- Chris Standaert: Right. We wouldn't recommend, there, there's no data to say that...
- Marie Brown: Right.
- Chris Standaert: ...this helps their health outcome at all.
- Kevin Walsh: So, we can get rid of the or... and everything after it. Well, we'd get rid of the...
- Craig Blackmore: No, we would say or women.
- Kevin Walsh: ...women, yeah. Thank you.
- Craig Blackmore: Younger women presumably, but. Alright, so, I mean, let's just...
- Marie Brown: OK, that's helpful.
- Craig Blackmore: So, I'm hearing sentiment that we not cover screening in men who aren't in one of these special populations, right?
- Michelle Simon: Did you want to put...
- Marie Brown: Correct.
- Michelle Simon: ...9.3 on there or not? There's no percentage. Fracture risk calculated by FRAX.
- Craig Blackmore: Well, that's implied... well, yeah.

Chris Standaert: 9.3 is from FRAX. So, just, I don't know how... if we'll keep the same number. We may just tear it off at... may just rank it equivalent to 65.

Michelle Simon: OK. That's fine.

Craig Blackmore: So, I'd get rid of the 9.3.

Michelle Simon: [inaudible]

Craig Blackmore: We can use the wording that the USPHS uses maybe? Maybe, well we don't know...

Marie Brown: They used...

Craig Blackmore: ...their exact wording.

Marie Brown: ...they used the 9.3.

Craig Blackmore: So, I want a... I want a show of hands. I'm... I'm hearing some sentiment that... that we shouldn't be doing the screening in... in men.

Kevin Walsh: Men without risk factors.

Marie Brown: Men without.

Carson Odegard: Men without, men without.

Chris Standaert: But there's no data.

Craig Blackmore: Right, but what about, where are we going to get into the high risk because of steroids and all this?

Chris Standaert: Through special populations.

Craig Blackmore: Through special populations?

Chris Standaert: Sorry, this would be asymptomatic people. So, they don't have a fracture.

Craig Blackmore; Yeah, but you can be asymptomatic and taking high dose steroids for your inflammatory bowel disease, and then we'd get up over 9. So...

Kevin Walsh: So, let's just put...

Craig Blackmore: ...that'd [inaudible].

Chris Standaert: [inaudible] to call them out.

Kevin Walsh: ...asymptomatic and low risk.

- Craig Blackmore: Yeah, but I mean, if we just say men who... who achieved that same threshold, the only way they're going to get there... although that wouldn't be covered in the FRAX.
- Chris Standaert: So, if you leave this as just...
- Craig Blackmore: That doesn't work.
- Chris Standaert: ...asymptomatic...
- Craig Blackmore: Never mind.
- Chris Standaert: ...women or younger women, this only applies to women, right? So, then our only condition for men is going to be men can be screened if they have zing.
- Seth Schwartz: Yeah, I think it makes more sense...
- Chris Standaert: Yeah, make it less...
- Seth Schwartz: ...to organize...
- Chris Standaert: ...so we don't have an...
- Seth Schwartz: ...it that way.
- Kevin Walsh: My only question is, does FRAX have... have input for things like steroid use and other medical conditions and whatnot?
- Christopher Shurhart: It has...
- Michelle Simon: Yeah, glucocorticoid.
- Christopher Shurhart: ...it has binary inputs for seven clinical factors.
- Michelle Simon: Yeah. So, it's age, sex, weight, height, previous fracture, parent fracture at hip, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol three or more units per day.
- Christopher Shurhart: So, are you, the point is, are you capturing those things in the FRAX so you don't necessarily need to pull out steroid use or whatever? It's already in the FRAX, and then you go... and then you have just this... the straightforward risk number.
- Craig Blackmore: I mean, I would prefer that.
- Christopher Shurhart: So, once again, some of the details, the plumbing of FRAX, there is clearly a gradient of risk for steroids. The more you take, the longer you take them, the higher fracture risk. FRAX does not take that into account. It's a threshold value.
- Michelle Simon: [inaudible]

Christopher Shurhart: Yep, just, the same thing as smoking. There's a dose-response relationship in alcohol. Those are all binary values in FRAX, and I just did a calculation using, just to see... to get to that 9.3 threshold if we could get there somehow, 80-year-old man at 69 inches tall and 150 pounds has a 10% major osteoporotic fracture risk.

Michelle Simon: [inaudible]

Christopher Shurhart: Yeah, I mean, there's a distribution of, yeah... median versus distribution, yeah, and that's Caucasian, too. They are substantially lower risk for African-American, Hispanic.

Chris Standaert: The majority of the population isn't 150 pounds, either.

Craig Blackmore: OK. So... so I think we're fairly happy around this framework for women, and then we have sort of conflicting approaches that we might consider for men. One is to use the same 9.3 threshold, which you can get at in FRAX by clicking the steroid button or the... maybe in some isolated cases of older, thin white men. So, one approach would be just to use that same threshold. A second approach would be to say not in sort of normal risk men but in men who have specifically defined conditions that we... that we list, which would include things like steroids or, you know, hypo-... androgen... androgen deprivation, yeah, which I don't think is in the FRAX explicitly. So, what's the preference? Just list them or defer to FRAX or list them and defer to FRAX?

Michael Souter: I don't think we can use the FRAX tool because it's based on the, you know, as it said the...

Craig Blackmore: You do not or you do?

Michael Souter: ...I do not think we can...

Craig Blackmore: Do not.

Michael Souter: ...use the FRAX tool. I would favor that we specify male gender associated with a list of conditions that puts him at risk, and one of the...

Craig Blackmore: OK.

Michael Souter: ...considerations I have for that is that I think that the consequences of fracture in males are different from that in females. The mortality is higher. So, I think that, you know, we have to take that into account. I don't think we can use the same stratification level.

Craig Blackmore: OK, is that... do other people agree with that, or? I'm seeing a few nods. Can I get some shakes or nods? I'm seeing a lot of nods, OK. OK, so we need to define the clinical scenarios where DEXA might be acceptable. So... we've heard some and one was long term corticosteroids, not just pulse dose but some sort of long term corticosteroids, we heard. We heard some sort of...

Christopher Shurhart: This is for men?

Craig Blackmore: Men, yeah.

Christopher Shurhart: Yeah, previous fragility fracture.

Craig Blackmore: No, yeah, known fragility fracture.

Richard Phillips: [inaudible] disease.

Marie Brown: Then that's a disease.

Craig Blackmore: We're in the, we're in the...

Kevin Walsh: But you're not screening, but...

Michael Souter: It's a diagnosis then.

Craig Blackmore: We'll cover that later.

Kevin Walsh: But how do you get to glucocort-... why are you using high... don't you have to have another preexisting diagnosis to be using high-dose glucocorticoids?

Craig Blackmore: Yes, and I don't know what it is, but if you're on high dose glucocorticoids you're [inaudible]

Kevin Walsh: So. OK. It seems like an artificial distinction to me.

Craig Blackmore: Well, it may, it may be, but we got to have some kind of framework to get through this. So, long term glucocorticoids.

Marie Brown: Do we really need... then there's going to be debate about long term. Why don't we just say, glucocorticoid use?

Craig Blackmore: Because every time you get a bad cold and a long cough you get put on pulse dosed steroids for a week and then...

Marie Brown: Well, then do you think that people would actually... once they've been on...

Craig Blackmore: I have no idea.

Marie Brown: ...steroids for a week. It's hard to imagine that.

Chris Standaert: The FRAX says greater than three months. [inaudible] greater than three months.

Christopher Shurhart: Five milligrams or more for greater than three months, 450 mg prednisone equivalence lifetime is what FRAX uses.

- Craig Blackmore: I like it.
- David McCulloch: That's totally reasonable. It's like [inaudible] information.
- Craig Blackmore: Alright. So, when you... when we finalize this, if we could incorporate the FRAX definition of steroids, but we're going to move on. What else is in the FRAX, well... no, forget the FRAX for now. So, what are the other conditions we talked about?
- Richard Phillips: The use of...
- Craig Blackmore: Androgen...
- Richard Phillips: ...[inaudible] for prostate cancer had a risk.
- Craig Blackmore: So, androgen suppression...
- Richard Phillips: Hypogonadism, or treatment of that.
- Craig Blackmore: Androgen, androgen deprivation.
- Christopher Shurhart: Some, some people use the term hormonal manipulation.
- Craig Blackmore: Hormonal manipulation.
- Richard Phillips: Sounds good. Does that include transgenders?
- Christopher Shurhart: I'm just... so actually it, it does. So, those patients, for instance, transgender patients who receive... it depends on, you know, what the transgender change is, but antiestrogen therapy also are at high risk.
- Richard Phillips: Interesting.
- Christopher Shurhart: Yeah.
- Craig Blackmore: OK, other... other... what are we missing on here, what else? Rheumatoid arthritis shows up in the FRAX, is that right? I'm happy including that.
- Kevin Walsh: There's something about malabsorptive...
- Michelle Simon: CMS uses...
- Kevin Walsh: ...conditions or something like that.
- Michelle Simon: ...hypothyroidism.
- Craig Blackmore: Malabsorptive conditions.
- Kevin Walsh: Yes, that stuff.

- Craig Blackmore: Yeah.
- Kevin Walsh: I think that was one of the categories.
- Craig Blackmore: Yep.
- Chris Standaert: Did neurological disorders show up, people who developed muscular dystrophies and other things who were in the neuromuscular population?
- Craig Blackmore: Neuromuscular? You would think so.
- Richard Phillips: The other thing, wasn't age over 85 seemed to fall out, too, as being at pretty high risk, but I'm not sure if I make it to 85 I'm happy not to take anything, but I... but I still think I met the criteria, you know, the number needed to treat was pretty small.
- Craig Blackmore: Well, according to FRAX, age 85 would not put a normal-sized person, male, at risk, although maybe a tall, thin male.
- Richard Phillips: I'm trying, looking for that.
- Craig Blackmore: Do we want age 85 on there or not?
- Group: No.
- Chris Standaert: Is... is the neurologic... is the neurologic stuff in FRAX?
- Michelle Simon: Neurologic?
- Chris Standaert: Neurologic stuff, so people who have a neuromuscular disease who are clearly at risk for... I assume people with neuromuscular disease are at risk for osteoporosis.
- Craig Blackmore: So, other payers list primary hyperparathyroidism, celiac sprue, radiographic signs of osteoporosis or low bone mass, which is radiographic... radiography is terrible, hypogonadism, ADT...
- Christopher Shurhart: Androgen deprivation therapy.
- Craig Blackmore: Androgen deprivation, OK.
- Michelle Simon: Hypothyroidism is in CMS.
- Craig Blackmore: Is in CMS?
- Michelle Simon: Yeah.
- Craig Blackmore: Where's CMS, I don't see CMS.
- Christopher Shurhart: Hypothyroidism?

Michelle Simon: Hypothyroidism, well that's what it says. Slide 25 on the evidence report.

Christopher Shurhart: That would not be typical.

Kevin Walsh: Hyper?

Christopher Shurhart: Hyperthyroidism, yes. Hypothyroidism, no.

Michelle Simon: Maybe it's a misprint. It says hypo. I don't know.

Christopher Shurhart: It might be a misprint, maybe it's a typo.

Kevin Walsh: Slide 40.

Christopher Shurhart: I'll double check.

Michelle Simon: Slide 25 I was looking at. It's all the screening. [inaudible] examples.

Christopher Shurhart: So, there's some potential resources to develop this list. I mean, the National Osteoporosis Foundation has a set of secondary causes of low bone mass. It's quite extensive, but it certainly could be a basis for extraction for...

Seth Schwartz: Can we just say something like that... so underlying cause of secondary risk for low bone mass or something like that?

Chris Standaert: Right.

Seth Schwartz: Without specifying all the conditions.

Chris Standaert: So, list a few...

Michelle Simon: Right.

Chris Standaert: ...and then say... that we clearly think so... there was the first three we clearly think are important, and then the rest you say other conditions known to be associated with low bone...

Richard Phillips: Right.

Chris Standaert: ...low bone mass.

Richard Phillips: Right.

Chris Standaert: Other medical condition.

Craig Blackmore: Might be more realistic than trying to...

Michelle Simon: Than trying to nail everyone.

- Christopher Shurhart: Lumping versus splitting.
- Chris Standaert: Yeah.
- Seth Schwartz: Of course, I need to ask the question, does bisphosphonate therapy make any difference in these subgroups?
- Christopher Shurhart: Are you asking me?
- Chris Standaert: Well, I think...
- Seth Schwartz: Do we have any data, I mean, I guess I'll ask our vendor, do we have any evidence of... on efficacy in any of these subpopulations?
- Michael Souter: But we're not looking at bisphosphonate therapy.
- Chris Standaert: No.
- Seth Schwartz: Or just any treatment.
- Michael Souter: There's a whole list of other, there's a whole list of other treatments that could be...
- Seth Schwartz: Fair enough. So, I guess, any... any treatment to... any treatment that prevents low...
- Chris Standaert: Right, so in these...
- Seth Schwartz: ...fracture risk in these... in these subpopulations?
- Chris Standaert: But in these populations, what we're also trying to do is define their fracture risk. So, this is the treatment they have. This is the disease they have. What is their fracture risk, and will that change how I manage them? Do I give them a cane? Do I give them a walker? Do other things help mitigate their fracture risk, not just treat their bone density or do I have to alter the medical treatment I'm giving them because I've plummeted their bone density too far that I can't keep giving them corticosteroids anymore? Using these... I think that's how you're using these more in this population, as opposed to screening for bisphosphonates.
- Seth Schwartz: Then we're not talking about screening anymore, right?
- Chris Standaert: No, we had this conversation earlier, yeah.
- Seth Schwartz: OK, sorry.
- Chris Standaert: Yeah, we're not really talking about screening.
- Craig Blackmore: We're going to use the term to make life simpler, but we're not really talking about screening. OK, so, are we happy with this? OK. OK, so now how about

maybe we'll move back to the women and talk about repeat screening intervals, another simple question. So, so let's go below, right above monitoring, let's make a new bold thing that says repeat screening. I just don't want to screw up what's already written there, excuse my language. So, we do have data on rapidity of progression of osteoporosis, or at least rapidity of progression in lower bone mineral density. So, what... where do you want to go with this? Who wants to take a stab?

Kevin Walsh: I would propose that we use the Gourlay numbers.

Craig Blackmore: OK. So, where are you?

Kevin Walsh: Looking for Gourlay.

Michelle Simon: Slide 31.

Craig Blackmore: Slide 31.

Michelle Simon: Of the evidence report.

Craig Blackmore: So, Gourlay said if you start off normal, you take between 11 and 25 years to reach... it takes between 11 and 25 years to develop osteoporosis or fracture. If you start with a T-score of 1 to 1, -1 to 1.5, it takes 14 to 21 years. If you start with a T-score of -1.5 to 1.99, it takes four to five years, and if you start with a T-score of -2, it takes about a year.

Teresa Rogstad: That... that's for 10%, right?

Chris Standaert: Right. So, but this doesn't... am I reading this wrong? This doesn't talk about the value of rescreening. This tells you the predictability from your initial screen, and so this doesn't say that you rescreen at 4.7 years, you rescreen... this says that if people have a T-score of -2 to -2.49, they...

Christopher Shurhart: It, it's an inference.

Chris Standaert: ...they are going to reach the threshold where...

Christopher Shurhart: Right.

Chris Standaert: ...10% of those women will have...

Christopher Shurhart: Which is when you would start screening in the first place.

Craig Blackmore: So, it's sort of like what's the yield.

Chris Standaert: That's when you start...

Craig Blackmore: It's the yield of subsequent screening, and... and for... the yield doesn't reach 10%. In other words, 10% of the people don't convert to that -2.5 threshold until you get 17 years.

Chris Standaert: So it's the time until the person...

Craig Blackmore: Until 10%...

Chris Standaert: ...10% of the women.

Craig Blackmore: ...of the people.

Christopher Shurhart: Get to the threshold.

Craig Blackmore: Get to the threshold where you would start, basically start treating.

Seth Schwartz: And is that based on DEXA scans in the follow-up of this study?

Christopher Shurhart: Yes.

Seth Schwartz: OK.

Christopher Shurhart: So, you could simplify this and say that you retreat... if your T-score is less than 1.5... greater than -1.5, you use 17 years, you use five years if it's 1.5 to 2, and if it's greater than 2, you use one year.

Seth Schwartz: Why would you use it if it's one year, I mean...

Chris Standaert: You just treat them.

Seth Schwartz: Why don't you just treat them? If they're 2 to 2.5, I mean.

Craig Blackmore; Well, that would only be 10% at one year. So, 90% at one year would still be normal.

Chris Standaert: Yeah, so the idea of... so what this doesn't tell me is... is... I sort of get it, but so... like... you have advanced osteopenia. You have a T-score of 2 to 2.5. In one year, you're going to be at this 10% threshold where you should go screen them?

Craig Blackmore: No.

Chris Standaert: We already know... but that's what we're saying. We already...

Craig Blackmore: We're saying that in that group...

Chris Standaert: Right.

Craig Blackmore: ...if you screen them again in a year...

Christopher Shurhart: 10%.

Craig Blackmore: 90% are still normal.

- Chris Standaert: Right.
- Craig Blackmore: But 10% you're going to start treating.
- Christopher Shurhart: So, if you accept a number needed to treat of 10, then you would treat.
- Craig Blackmore: Then you would treat.
- Chris Standaert: Then you just treat them, but I... I...
- Craig Blackmore: No. Because the number needed to treat for the treatment is much higher than 10. It's the number needed to screen.
- Chris Standaert: So... so what... so if you have this... so in one year if you have a T-score of -2.2, in one year, 10% of those women will now have a T-score below 2.49, so they're...
- Craig Blackmore: Yes.
- Chris Standaert: ...now osteoporotic.
- Craig Blackmore: Yes.
- Chris Standaert: That's what this is saying.
- Craig Blackmore: Yes.
- Chris Standaert: And so is that... that... but then if we say you should rescreen one year later, you're saying that test is going to be the hard trigger to treat them. You're going to wait that one year and when those 10 people become technically osteoporotic or have broken, we will then screen... scan them and treat them, as opposed to you know that 10% of the people are going to be at that, you're going to be there in a year, so you just treat everybody. We're going to say do it one more time in a year.
- Craig Blackmore: So, then you might as well treat everybody without... as soon as you... you might as well treat us all.
- Chris Standaert: Well no, when you get...
- Craig Blackmore: Because we're all, at some point we're going to get.
- Chris Standaert: No, I'm just, I'm, I'm...
- Seth Schwartz: No, but, but he's, he's extrapolating backwards. He's taking your point and... and... and applying it to the whole idea of screening in the first place.
- Chris Standaert: Right.
- Craig Blackmore: So, we, we have...

- Seth Schwartz: And what we're saying is no. We don't think that giving 100% of people some therapy forever makes sense. We want to identify the group of people who are at higher risk.
- Chris Standaert: Right.
- Craig Blackmore: So, implicit in our 9.3% threshold is some number needed to treat.
- Chris Standaert: Mm-hmm.
- Craig Blackmore: So, we have decided, as a society, that when... when the fracture risk is 9.3%, the number needed to treat with bisphosphonates or whatever is appropriate. So, what this is telling us is that if we rescreen at a year and the person with the -2.2, 10% of those people at a year will have reached the treatment threshold where the number needed to treat is appropriate. If we treat them all at 2.2, our... our number needed to treat would be 10 times the threshold that we thought was appropriate, right?
- David McCulloch: Yep, that's exactly right.
- Chris Standaert: Where was... where was the number saying treating less, rescreening less than two years? Because we were looking at that number somewhere.
- Michelle Simon: That was the, that was the Frost Study, the page before.
- Teresa Rogstad: Well, I think you might be thinking of this slide based on the...
- Michelle Simon: Yeah.
- Teresa Rogstad: ...Australian study.
- Craig Blackmore: So, this is the Frost.
- Teresa Rogstad: They used a different model.
- Michelle Simon: The authors in this study also say there are some limitations on their study and that all of the people in the study were volunteers, and they think that they're probably likely to be healthier than the average population. They also had no comorbidities, any of these people.
- Chris Standaert: Which one, the Frost Study?
- Michelle Simon: The Frost Study.
- Teresa Rogstad: The Gourlay model was also adjusted for risk factors, most of the ones that are in the FRAX tool was a little more fine-tuned.
- Craig Blackmore: So, I don't have a problem with the Gourlay simplified. I might make it 15 years instead of 17 years because it's a round number, but I'm happy with 17 and

then when you go, if you're between 1.5 and 1.99 you bring it back in five years, and if they're 2, -2, you bring them back in a year, which I think is what you're saying. I certainly welcome other suggestions.

Seth Schwartz: I guess my only... my only point in this is, this is in a 67-year-old woman or older. Not any of the other groups that we talked about.

Richard Phillips: Right.

Seth Schwartz: So then what you're talking about is 17 years. You're talking about an 84-year-old woman and is there any value in rescreening an 84-year-old woman? I mean, I'm not sure.

Craig Blackmore: Well, she might still be normal.

Michelle Simon: 90% of them are.

Seth Schwartz: But can we extrapolate... but can we extrapolate this to the other populations that we've talked about, younger woman with the same risk group or the men that we just talked about?

Chris Standaert: And...

Craig Blackmore: I don't, I mean, I don't know.

Chris Standaert: ...do these people who are at the tease of 2 to 2.5, so they stayed... so 10% dropped below, the other 90% don't. Do they get screened every single year?

Craig Blackmore: They could.

Chris Standaert: Do you just keep doing it? I mean, because 90% of them are not going to be there, and then you're going to have the same thing. They're going to get screened every single year.

Craig Blackmore: Yeah. Your number...

Chris Standaert: So, you keep waiting...

Craig Blackmore: ...your number needed to screen is 10.

Chris Standaert: ...for the... you're waiting for the...

Craig Blackmore: Except you're not really screening, but yeah. It seems silly in a way.

Marie Brown: I would end up wondering more about what we do [inaudible].

Craig Blackmore: Thoughts from this side of the room?

Marie Brown: To... to do that we'd... we'd be doing more DEXAs than we do now.

Chris Standaert: Right.

Craig Blackmore: Oh, I don't think so. You're only... I mean this is only a small group of people. This is a...

Michael Souter: Fragmental, we're talking about really small.

Craig Blackmore: ...this end of the bell curve.

Carson Odegard: Yeah. So, you're not going to be doing that much.

Chris Standaert: I guess that would be in the absence of treatment, too. So, if you choose to treat them...

Carson Odegard: Well, then it's monitored.

Craig Blackmore: And then you're...

Chris Standaert: Right, because either...

Christopher Shurhart: I... I would just say, these are much...

Chris Standaert: ...these people aren't...

Christopher Shurhart: ...tighter than any of the agencies. I mean, this is... this is tight.

Craig Blackmore: This is restrictive.

Christopher Shurhart: This is very restrictive.

Richard Phillips: Yeah.

Christopher Shurhart: So, you're talking about more studies but right now they're doing 1000 times more studies. It's every two years no matter what your score is.

Richard Phillips: I don't think there are guidelines to talk about these screens and monitoring.

Craig Blackmore: I don't know...

Richard Phillips: After the fact.

Craig Blackmore: ...U.S. Preventive Services.

Teresa Rogstad: The guidelines say anywhere from one to five years, and it seems to be a little bit of an expert opinion type recommendation, and the taskforce made no recommendation...

Richard Phillips: Right.

Teresa Rogstad: ...in screening intervals.

- Chris Standaert: And the FRAX doesn't help us at all either. As people's risk profile changes if they age or other things happen to them. So, your T-score of... what do you do with a T-score of 1.5 if something happens to them on the way to change their risk profile?
- Craig Blackmore: Well, we could say...
- Chris Standaert: They go on steroids.
- Craig Blackmore: ...yeah, repeat.
- Chris Standaert: If they come out with RA at 68 years old and they go on steroids.
- Craig Blackmore: We could say or, you know, or interval development... or... one of the conditions that contribute the low, the ones we talked about for... for the guide. I mean, I think that's legit, right? You, you don't want to wait 15 years of just...
- Chris Standaert: No, that's something...
- Craig Blackmore: ...someone on steroids.
- Chris Standaert: ...you have somebody who has a pretty good bone at 67 and then gets RA at 69 or 70 and stick them on steroids for PMR or whatever.
- Craig Blackmore: We... we wouldn't this to be interpreted as you can't have another one because you had it. So... so we would need the qualifier.
- David McCulloch: Well, yeah, I mean, if you... if you... if something changes then you go into one of those... those special categories then...
- Chris Standaert: Right.
- David McCulloch: ...you meet those criteria. I think there are [inaudible] following some simplified... simplified version of Gourlay, because it... it is... it is based on natural history of likelihood of progression of bone density in... in a population and so, you know, if you've got a... just a... as you said, Craig, if you've got normal to mild osteopenia, chances are in 15 years, only 10% of those people would progress... the... the idea of saying they should all be screened every two years seems over... over-screening, but if you've got, you know, moderate between 1.5 and 1.99, then you're screening every five years, and if you have a high risk then screening every year. I mean, that... at least we could do, it's as Kevin said, it was strict but it's based on the best data we have.
- Craig Blackmore: It's based on what we have. So, I do think we should add the... if you scroll up, I don't know who's got it, Margaret over there. Yeah, that lot... that last bone... the last point under men where it says other conditions known to be associated with low bone mass, if you can cut... copy that and put it under repeat scoring... repeat screening. So, and then before... before the word other if you could put initiation of medications or...

- Chris Standaert: Or development.
- Craig Blackmore: Or development of.
- David McCulloch: Initiation of treatment?
- Craig Blackmore; Initiation of medication or development of other conditions known to be associated, is that...
- Marie Brown: Well, you'd have a... if you have to... to treat them you'd have to have the condition. So, you could just say having the condition.
- Craig Blackmore: No, no, no.
- Chris Standaert: [inaudible] of other conditions.
- Craig Blackmore: There are... there are medications that cause low bone mass, and there are conditions that... that develop that cause low bone mass.
- Seth Schwartz: I... I think you need to... I think you need to clarify what the word medication means, because it could be interpreted to mean that you started people on...
- Craig Blackmore: Oh.
- Seth Schwartz: ...on drugs.
- Craig Blackmore: OK, so indicating... initiation of medicine known to be associated with low bone mass or development of a condition.
- Seth Schwartz: Or say initiation of [inaudible].
- Chris Standaert: You could probably just say use of, because I could see you... I guess if he's screening somebody at 65 who, again, has RA and has had RA for two years and is now on steroids and you screen them and they are still pretty good, you're not initiating the start where you actually did it, but they're on steroids.
- Craig Blackmore: Right.
- Chris Standaert: And you're going to want to... so it's you using them, it's not... it's not a timing thing.
- Craig Blackmore: So, it's not initiation, it's use.
- Seth Schwartz: But then at what interval, because it, again, we don't want to just do it immediately. So, it's then or at two years, or at...
- Craig Blackmore: I feel like this is such a small group.
- Kevin Walsh: There's no evidence.

Craig Blackmore: I don't even want to specify. I don't, you know, if...

Kevin Walsh: Yeah.

Michelle Simon: You could just say the presence...

Craig Blackmore: If they want to screen the RA people every...

Seth Schwartz: Right.

Craig Blackmore: ...year, I don't have any reason to believe that...

Kevin Walsh: [inaudible].

Chris Standaert: I would read that as just, you have a population who's at risk and you're just worried about their density at some point, and you want to check a DEXA for whatever reason is what we're sort of saying, that you can repeat the screen in these people who have problems at your... we're not putting a parameter on it.

Craig Blackmore: I wouldn't know what to say.

Michelle Simon: You could just say presence of medication or conditions known to be associated with low bone mass.

Marie Brown: Rather than use?

Craig Blackmore: It's fine.

Michelle Simon: The conditions are tighter but [inaudible].

Richard Phillips: Yeah.

Seth Schwartz: Just get rid of other. Just get rid of other.

Chris Standaert: Just get rid of other. Make it singular.

Craig Blackmore: OK, that's actually easier than I thought it would be.

Richard Phillips: Is that last one to be associated with one year, or is that...

Craig Blackmore: Where are you?

Richard Phillips: ...where all the others are like the first one is 15 and then five years and then one and then use of medications there's no time interval.

Craig Blackmore: Right. So, she moved it out. Yes. OK. So, then the next issue is... what about people that have a fracture. So, you're chugging along, you're doing fine and then suddenly you have a fracture. What... what do we feel about the use of DEXA in this group? On one hand it doesn't seem to make sense, because they

have osteoporosis as diagnosed by their fracture, but we've also heard that in some clinical scenarios, the fracture may not be associated with sufficiently low bone mineral density that somebody might choose not to treat, even though there is a fracture.

Chris Standaert: I guess the other question I have looking at that is, if you have somebody who you diagnosed with osteoporosis, or you decide to treat them for their osteoporosis, we haven't talked about sort of... we haven't gotten there yet. I'm on a different thing than you are where you screen, you're basically tracking their response to treatment, right?

Craig Blackmore: That's where we... we're monitoring.

Chris Standaert: So, you put someone on bisphosphonate, and then you're monitoring treatment, but you've already... many of the people who are on treatment have already been diagnosed with osteopenia or osteoporosis and so are we... they therefore have a condition known to be associated with low bone mass, because they have it. Are we therefore allowing people to screen as often as they want to monitor for responsiveness to... does that language not allow that? Are we going to... are we going to specify that you can't use this to monitor response to bisphosphonates? I don't know.

David McCulloch: Well, I actually... I like what the agencies have said that once you've... once you've decided to treat, either because of a fragility fracture or you've met the threshold by all the stuff we've said, you're treating for osteoporosis. You should be on bisphosphonates and trying to keep people on it the best they can, do everything else to keep them healthy. There... there is no value, despite what the [inaudible] I mean, I get it. Doctors love to do tests and they love to do numbers and patients want to do numbers. Can you tell me next month whether my DEXA's better or worse, and we'll follow it and you start tracking, but the evidence would say, once you reach a fracture, if the goal is to reduce fracture risk, you're on treatment... we shouldn't be... I don't think there's any evidence that says that we should be covering to repeat DEXA scans to tinker around with doses and change things based on that. There isn't any evidence that that changes your fracture risk. If I can just... it... it's very similar to the transition that has been made in the past 10 years certainly in how we think about treating coronary artery or risk of future cardiovascular disease. I mean, there is still a lot of people in the community that will screen people with annual LDLs and then they decide to treat them and then they'll track the LDL and patients want to know what... what their cholesterols are over time. The consensus now is, no, you can use an LDL... among other things, to identify is this person now at sufficient risk to be treated with a statin? Once you... once you make that decision you don't need to... you don't need to check LDL. You don't need to check LFTs. You just treat them with a statin and... I... I think this is similar. You know, it's reasonable, I think what we're, what we've described is very reasonable for how using DEXA in... in asymptomatic people, blah, blah, blah, once you... to me, once you make the decision to treat somebody, you just treat them and the... certainly if... if an individual patient wants to have their DEXA done every month, then they can pay for it, but there isn't any evidence... I don't think the agencies should be... should be covering for ongoing monitoring

- with DEXA once you've started treatment, because I didn't see any evidence that... that suggests... knowing what the DEXA is... that changes your fracture risk. So, I would support what bullets four and... three and four on slide 30 of the agency recommendations.
- Craig Blackmore: OK. So, I'm just going to... to expand on that... I need... I need another circumstance up here. So, why don't you put after other risk factors in bold below that put monitoring treatment, which I think is what David's talking about. So, one suggestion we've heard is that, is that we shouldn't cover monitoring treatment. So, once you're diagnosed with osteoporosis and you're put on treatment, DEXA's done. Do we have other feel... different feelings about that... or is that... is that the... is that where the group is?
- Richard Phillips: What about if you have suspected failure while on treatment? Is that a reason to look at it again?
- Craig Blackmore: Well, how would you...
- Seth Schwartz: How would you suspect failure?
- Richard Phillips: That, that'd be a clinical decision. I mean, I...
- Seth Schwartz: But it's... what's it... how... what would a clinician base that decision on?
- Richard Phillips: That's... I'm... I mean... I'm putting it out as a question, you know, I don't know.
- Craig Blackmore: So, what circum-...
- Richard Phillips: You know, if somebody asks, maybe if somebody has a fracture, you know, while on treatment.
- Seth Schwartz: But that's not a clinical, I mean, that's...
- Richard Phillips: Because it might change...
- Seth Schwartz: ...that's an objective...
- Richard Phillips: ...would it change the treatment? I, I'm really not proposing this. I'm really playing devil's advocate here. I'm trying to figure out if we're really hitting the, hitting it straight.
- Craig Blackmore: So, I mean, one approach would be to say if you have another fracture we could do another DEXA to see if your bone mineralization is getting worse, and that might guide changes in treatment.
- Richard Phillips: You know, alteration...
- Craig Blackmore: I don't know.
- Richard Phillips: ...of treatment, I don't know.

- Craig Blackmore: I'm just...
- Richard Phillips: I don't know how often those occur. We're talking about, you know, pretty small numbers by now, I'm sure.
- Craig Blackmore: Those certainly occur but whether or not changing treatment helps prevent them from occurring is another question.
- Richard Phillips: I'm happy with it as it is, don't get me wrong, I just.
- Craig Blackmore: Any, any other thoughts on...
- Chris Standaert: Is there a time where somebody's medically... you have somebody on a bisphosphonate and you know their DEXA from two years ago and something changes about their health and you have to know more about their bone? I don't know. I don't know. Does that happen?
- Craig Blackmore: Well, clinical expert...
- Christopher Shurhart: Yes.
- Craig Blackmore: Is he...
- Chris Standaert: What circumstances would precipitate that?
- Christopher Shurhart: So, you have a patient on treatment?
- Chris Standaert: Uh-huh.
- Christopher Shurhart: We've already identified as high risk.
- Chris Standaert: Uh-huh.
- Christopher Shurhart: And there's high risk in high risk but the... the things that would make me think about reevaluating them, however, that might include DEXA, it might not, would be, steroids would be a common one. The initiation...
- Chris Standaert: They, they go on steroids.
- Christopher Shurhart: ...of steroids. The diagnosis of certain medical conditions.
- Chris Standaert: Right.
- Christopher Shurhart: You know, I could... there would be a dozen or two that I could think. So, there would be circumstances where in the intervening time, medical conditions would change and you would want to reevaluate.
- David McCulloch: So, but, they're already on a bisphosphonate.

Christopher Shurhart: Yes.

David McCulloch: You reevaluate, what are you going to do differently? Change them to a different bisphosphonate?

Christopher Shurhart: Potentially, yeah.

David McCulloch: Add something, I mean, I... I...

Christopher Shurhart: A different, not a different bisphosphonate another agent...

David McCulloch: ...or, I... I don't know.

Christopher Shurhart: ...another agent. Right, so for instance, for instance, osteoporosis diagnosed on bone density testing started on a bisphosphonate. Patient is two years into a bisphosphonate develops an autoimmune condition and starts on steroids. Retest that patient. Their... their bone mineralization has declined significant, let's say 5%. That would be a patient I would consider for a change in therapy. I might use an anabolic... in that patient, an anabolic agent, like teriparatide, and I would not necessarily do that based on the change with the addition of the steroid therapy alone. It would be the combination of the clinical factor plus the low bone mass, the change in the bone mass.

Kevin Walsh: And is... is that based on any data, or is that just...

Christopher Shurhart: No, that's me.

Kevin Walsh: ...clinical expertise?

Christopher Shurhart: That's me.

Kevin Walsh: OK.

Craig Blackmore: So, I guess the question is, there might, there might be some unusual clinical circumstances where somebody who deals with a lot of patients with osteoporosis might use this information to change treatment and... but I think... I think what I'm hearing is that the committee sees that as not the... the norm and we shouldn't just be doing routine DEXA follow-ups on patients because they are on treatment.

Michelle Simon: Right.

Craig Blackmore: So...

Marie Brown: That's the most important thing.

Craig Blackmore: ...we could just say no or we could try to allow for some flexibility, I guess, and I'm soliciting some input from the committee.

- Marie Brown: Well, maybe it's the development of a new condition that would increase the risk. That would be the only time we'd cover follow-up.
- Kevin Walsh: I, I don't think we saw evidence to...
- Craig Blackmore: Well, we didn't see evidence at all, it's just...
- Kevin Walsh: ...I thought that's why we were here. I'm sorry.
- Chris Standaert: It just went by really quickly, that's all.
- Craig Blackmore: You know, it's just, it's how far into the weeds of unusual clinical scenarios.
- Chris Standaert: So, if we, if we use what the agency said, once treatment for osteoporosis has begun, serial monitoring is not indicated. I think that's true.
- Marie Brown: Yes, that's true.
- Chris Standaert: And I suspect also that leaves some window, if somebody says, you know, I'm not doing serial monitoring, they've got polymyalgia rheumatic, they're on acute steroids, I want to know if their bone is gone so I... can I keep them on this or not, I want a DEXA. I think that's a fair question.
- Michelle Simon: Yep.
- Chris Standaert: I could see it happening on a very rare circumstance, but I don't know that this statement would preclude that.
- Marie Brown: I like that statement.
- Margaret Dennis: Medicaid, we, we allow exceptions to rules. So, if there's a compelling clinical reason, we're going to wave, you know, this decision and say absolutely, that makes sense. It's the next reasonable step in care. So, from that perspective, it... it wouldn't be that that could never happen. We'd look at it individually if they were a request.
- Michelle Simon: But that's...
- Chris Standaert: On slide 30, that's what they said...
- Craig Blackmore: OK, I mean, are we, are we happy with this? I'm seeing a lot of nods.
- Michelle Simon: Mm-hmm.
- Chris Standaert: The agency slide 30.
- Craig Blackmore: So, what about... well I'll let her write that down. I would change indicated to covered. OK, and then... yeah. We're done with that if you've got. I... I want to see it.

- Chris Standaert: We're done, right?
- Craig Blackmore: We're done. There we go. So, if we could just write the words once treatment for osteoporosis has begun, comma, serial monitoring is not covered.
- Christopher Shurhart: Can I ask a clarifying question from over here?
- Craig Blackmore: Yes.
- Christopher Shurhart: What would happen if you were a practitioner approaching the end of a course of therapy, because we probably will have some discussions, if we have not already, about duration of therapy? Would you consider a bone mineral density at the end of therapy to reestablish a risk profile as serial monitoring or not?
- Craig Blackmore: Well...
- Christopher Shurhart: That would be a common scenario, not an uncommon scenario.
- Craig Blackmore: Common scenario.
- Marie Brown: Because of the five-year use a lot of people have.
- Chris Standaert: I mean the...
- Christopher Shurhart: Because of some...
- Chris Standaert: ...but the problem...
- Christopher Shurhart: ...notion about the way the medications work and don't work over a period of time.
- Chris Standaert: ...but the problem you have is, again, this is... this is confusing what this tests does, right? The test predicts risk, and you're using bisphosphonate to alter the risk...
- Christopher Shurhart: Right.
- Chris Standaert: ...rate, though you don't use it to...
- Christopher Shurhart: Alter the risk.
- Chris Standaert: ...necessarily alter the results of the test, and so therefore doing it for five years and retesting doesn't really tell you whether it's effect... been effective or not. What tells you if it's been effective is one, they haven't broken and two, you cross your fingers and hope it's been effective because you're playing population statistics with a drug and so I... how does the new... if nothing has changed about their medical status, how does that test at five years help you? It's sort of curious, because you could do it at five years, because you... we already said that if you're in this zone where you have a low T-score, you can do it more frequently. I guess that's just screening though.

- Richard Phillips: That's screening.
- Chris Standaert: But yeah, I guess... so how does that... you would treat them... but how does it help you? Is it... they're... they're different things. It doesn't... the... the DEXA doesn't tell you whether or not the bisphosphonate made their bone more... more resilient to fracture.
- Craig Blackmore: I guess we would...
- Chris Standaert: That's my understanding...
- Craig Blackmore: ...we would want to see evidence that... that that evidence that...
- Chris Standaert: ...yeah.
- Craig Blackmore: ...post-treatment DEXA helps risk stratify. OK, if you could scroll up please where we get to monitoring. In this case, I don't know if monitoring is the right word but the first question is dealing with the scenario of somebody not known to have osteoporosis who presents with a fracture, and so the... sort of the conflicting perspectives here. One is while I need to confirm that the fracture was related to low bid... low BMD because we want to use that information to decide if we're going to treat that or the other flip side of that would be while the definition of fragility fracture is where osteoporosis is defined by the presence of the fragility fracture, so you should just treat it.
- Michelle Simon: It seems like it should not be indicated if there is this condition.
- Craig Blackmore: Should not, is that...
- Michelle Simon: Should not be covered.
- Craig Blackmore: OK, is there differences? Are we all in the same place?
- Marie Brown: Mm-hmm.
- Chris Standaert: So, this would apply... women over 65 already got screened. So, if they broke a year after you screened them that probably doesn't help you to screen them again, because now they have osteoporosis and even though your DEXA said they're good, there's still something bad about their bone that you've got to deal with, and the DEXA doesn't help you.
- Richard Phillips: Right.
- Chris Standaert: If nothing else has changed and no other medical thing. So, it wouldn't really apply to them. It would apply to... because younger people who break who aren't in that 65 and can... would have been screened. It applies to men who don't have a known medical condition, and I guess then do you... from the clinician's eye, if you had a male who came in with a hip fracture or a sacral fracture... sacral insufficiency fracture for no apparent reason other than

probably bad bone, does a DEXA help you or should you just do the medical workup for their bone? Does the DEXA really do anything there? You go, oh wow, they have... there's something wrong with their bone and I need to figure this out, because they're a 60-year-old male and they shouldn't do this, and does the DEXA really help you... I don't... we don't have any data that DEXA helps you, I don't think, but medically would you just sort of sort through what's... you have to go chase down their bone.

Craig Blackmore: I mean, I... so you're... you're supporting this?

Chris Standaert: I don't know. I don't know. I'm just... I'm... I'm... I'm wondering how this plays out is what I'm wondering. So, circumstances where you have a fracture, where you know nothing about bone density already. How does... how do you then think about bone density in that patient, and does it help you at all, or does it... is it already... you're already... it's just another marker. I know they broke. I know their bone's bad. I... you have to treat it or figure out why, and it doesn't really matter what the DEXA tells me.

Christopher Shurhart: So, I can, if you'd like.

Craig Blackmore: Sure.

Christopher Shurhart: Just sort of tell you. So, for other fractures, particularly... I think you mentioned men so I can do that specifically and then more generally. Men are... are much more likely to have correctable causes of bone strength, not sort of bone, you know, osteoporosis but secondary factors. So, for a man who has a... another non-hip/non-vertebral fracture that is suspected by mechanism to be fragility, let's say... you just said a sacral insufficiency fracture, those patients, for me, and I see these patients, bone density is useful for me, because in a patient who has normal bone density, I am questioning whether or not that's a patient who will respond to treatment. In a patient who has osteoporosis, then, osteoporosis... that's not a classic osteoporotic fracture but osteoporosis may have contributed to the genesis and I would recommend treatment in that case. In a patient who has a bone density in the world between in ost... the osteopenic range, it would once again depend on risk factors and some particulars of the fracture, but in general, not all other fractures are osteoporotic fractures, even with low energy mechanisms. So, that way... the probability of it being an osteoporotic fracture increases when the bone density is lower. Does that help?

Craig Blackmore: Yeah, I mean... I guess I can see, you know, if a 40-year-old guy breaks a bone and you don't know why this might be a piece of information you need, but if you've got a 70-year-old woman who comes in who has never had a DEXA scan and she has an osteoporotic fracture, or she has a fragility fracture of her spine, it's osteoporosis, right, but, you know, yeah. There's... there... there might be some very unusual situation where you don't know what's going on. Something's wrong. Why does this, you know, why does this 30-year-old guy have this problem? So, I... I don't know if we need to go into that level of granularity or if it's covered under... under the same set of conditions. So, I

guess, what do the agencies say? In the setting of a fragility fracture, DEXA scan is not indicated to confirm the diagnosis of osteoporosis.

Chris Standaert: Do we have to comment on this? Is one of our questions dealing with the presence of a fragility fracture? I mean, do... are the conditions already cover this? Do we have to deal with this or is it already covered in everything else we've said? So, that guy broke something and you go, huh, something's wrong and you draw some blood and go oh wow, their testosterone's really low for a 30-year-old, I'm going to get a DEXA, you can get a DEXA. You suddenly found out they have hypogonadism, you can get a DEXA.

Michelle Simon: Mm-hmm.

Richard Phillips: Yeah, so it falls under the other category.

Michelle Simon: Right.

Chris Standaert: So, does it... does it fall under the other categories? Do we need a special callout saying you can't... we have... you can't do it for a fracture. If that 67-year-old hasn't had a DEXA and broke you still may want it, because you may want to know where they lie, even though it doesn't really help you. You know they have osteoporosis. If they had the DEXA three years ago and they're osteopenic and they broke, I mean, you're there. You have osteoporosis now. There's no point in re-monitoring.

Seth Schwartz: But isn't that the point that it doesn't help you, so why should we be paying for it?

Chris Standaert: Right.

Seth Schwartz: So rather...

Craig Blackmore: So...

Seth Schwartz: ...than leaving wiggle room, specifying that it's not covered in that situation would be...

Craig Blackmore: ...yeah, I think it...

Seth Schwartz: ...more in line with what it looks like the data is showing us.

Craig Blackmore: It sounds like it's sufficiently used for that indication that we... it would be helpful if we specify, I think.

Chris Standaert: Do we have any data one way or the other on this, on DEXAs in people who broke?

Teresa Rogstad: There was one study that we excluded from the report because... because it... because it wasn't a screening study. They did... I mean... it... it wasn't the population we were asked to look at it, but that study did show that screening

- in individuals who had had a fracture improved the risk of future fracture. I can give you some details.
- Chris Standaert: So, you can... in people who fractured and were screened, they had a lower risk of repeat fracture than people who weren't screened?
- Teresa Rogstad: Yes, right.
- Chris Standaert: But we don't have that data in our data report. That's why maybe...
- Craig Blackmore: Right, but... I mean, that was... that was this retrospective study looking at people who got a DEXA versus ones who didn't, and there's huge differences. I mean, you get a DEXA because you seek out care and, you know, it's the healthy volunteer bias. It's, it's...
- Teresa Rogstad: It... it's not the study that was mentioned in the public comments.
- Craig Blackmore: It's not the study.
- Teresa Rogstad: No, hold on a second. The... the... the patients were selected because they came into an orthopedic surgeon... surgery department for treatment of a fracture and... let's see... there are 458 of them, follow-up was six years. At the end of that time, the new... new incident fracture in the screened group was 18% and 29% in the unscreened group. Relative risk was 0.58.
- Craig Blackmore: They were randomized or they...
- Teresa Rogstad: Let's see, no. No, it was an observational study, historical controls. So, not a high quality study. There was some adjustment for confounders.
- Craig Blackmore: So, alright. So, maybe under monitoring treatment at the very bottom of the page, we could say development of a fragility fracture is not of itself a covered indication. Does that capture...?
- Richard Phillips: It's basically the same thing.
- Group: Yeah.
- Craig Blackmore: How about development of a fragility fracture alone is not...
- Richard Phillips: Yeah, yeah that's more clear.
- Craig Blackmore: OK, and then if you could remove the whole section that says monitoring and then scroll up and show us what we've got. OK. So, we... I'm going to just sort of summarize here on the record and make sure that we give this a last going over because it's important. So, could you scroll to the top please?
- Richard Phillips: Could I get... could you see that thing on FRAX again? It seems to me that it's a little ambiguous. Maybe I'm wrong. Didn't we have 9.3% before as a...

- Craig Blackmore: Right, so 9.3...
- Richard Phillips: ...threshold, but now I'm... I'm trying to figure out what the threshold is now.
- Chris Standaert: 9.3 is the equivalent to any fracture risk on FRAX.
- Richard Phillips: Oh, 10-year.
- Chris Standaert: And then we're just letting other... you're letting people use other tools to come to that same 10-year risk.
- Michelle Simon: Does it... just a question.
- Richard Phillips: And how are they, they're going to know that it's a 9.3%? I guess, I mean, I'm not...
- David McCulloch: Yeah, to... to make it clear, say younger women with equivalent 10-year fracture risk to women age 65.
- Craig Blackmore: So, after the word...
- David McCulloch: By FRAX.
- Richard Phillips: That's fair enough.
- David McCulloch: Yeah.
- Richard Phillips: That's... that's... that's I guess what I'm getting at.
- David McCulloch: Yeah.
- Richard Phillips: Yeah.
- Christopher Shurhart: Can I ask a... can I ask a question?
- Craig Blackmore: Yes.
- Christopher Shurhart: So, back to the callouts for men, those would be reasons to screen men. Would they not also be reasons to screen women or some variation thereof?
- Chris Standaert: Would they plug into the FRAX and wouldn't they give the woman the 9.3%?
- Christopher Shurhart: So, hormonal androgen deprivation does not... hormonal manipulation does not. They cannot be accounted for in FRAX. There's actually been some studies to show if the secondary osteoporosis button in FRAX might account for some of those, and it doesn't because they tend to... the changes in bone strength tend to happen relatively rapidly and a 10-year timeframe's not terribly sensitive in FRAX.

- Craig Blackmore: Well, what do the committee members think? Do we add the word men or women?
- Michael Souter: Well, you've got the asymptomatic women there. I suppose if they've actually got any of these conditions, are they still technically asymptomatic?
- Michelle Simon: They could be.
- Chris Standaert: Or they wouldn't be asymptomatic.
- Craig Blackmore: Yeah, I don't know. Technically we just need to be explicit.
- Marie Brown: Men or women would clarify it.
- Seth Schwartz: I think you're talking about a pretty small population of... of unusual women. I don't have any problem including them in that.
- Craig Blackmore: Well, that's where I am. I mean, I think our... our goal is not to deal with the 1%, it's to deal with the... OK. So, it's going to say men or women. People of any gender, would you prefer that?
- Chris Standaert: Yeah, adults.
- Seth Schwartz: Yeah, you don't have to specify.
- Group: Yeah.
- Craig Blackmore: She can say men or women, it's fine. OK, how about... let's look at these. This is our... this is our opportunity to make sure we're not making a mistake.
- Kevin Walsh: May I ask, maybe I missed this, what's screening/rescreening versus the rescreening below?
- Group: Those are rescreening.
- Craig Blackmore: Alright. OK, and then so...
- Marie Brown: Initial screening maybe.
- Craig Blackmore: Yeah. Initial, yeah, before the word screening, and then let's scroll down, please. Stop.
- Michelle Simon: I still think we can get rid of 'or' after use of medication if we get rid of associated with low bone mass, because we say it again in the second. So, use of medication or presence of a condition. They're both associated with low bone mass.
- Chris Standaert: Yes.
- Craig Blackmore: That's been bugging Michelle for the last hour. Use of medication.

Seth Schwartz: The problem was... the reason we included that is because you say use of medication... that could sound like bisphosphonate therapy or some other treatment.

Kevin Walsh: Put a comma...

Michelle Simon: But only if it's associated with a lone bone mass.

Kevin Walsh: ...after medication.

Michael Souter: I don't see anything wrong with injecting a few more words to ensure clarity.

Chris Standaert: Yeah, we'd rather...

Michael Souter: Rather than kind of possible misinterpretation.

Chris Standaert: ...yeah.

Craig Blackmore: Sorry.

Michelle Simon: That's OK.

Craig Blackmore: Alright, once treatment.

Chris Standaert: We're trying.

Craig Blackmore: Can we scroll to the bottom, please? Alright, we're going to go to the decision tool.

Carson Odegard: Can I... can I make a comment?

Craig Blackmore: Yes.

Carson Odegard: I think it would be helpful to clarify what you mean by hormonal manipulation.

Carson Odegard: What is your concern?

Marie Brown: Transgender.

Chris Standaert: Transgender individuals?

Carson Odegard: Yeah, I mean, that's just so nonspecific it could be interpreted oral contraceptive therapy, treatment of transgender.

Craig Blackmore: Well, why don't you...

Carson Odegard: What are getting at, something that is causing hypogonadism?

Michelle Simon: Or low estrogen.

Craig Blackmore: Why don't you just take out that line?

Marie Brown: And then the other covers anything.

Chris Standaert: Yeah.

Carson Odegard: OK. That's fine.

Craig Blackmore: Any other comments? OK, we'll go to the tool and... alright. So, we're familiar with the tool and a lot of the tool is really going through the principles upon which we make our decision and that they are evidence-based and that we base them on evidence of effectiveness, as well as safety and cost, and the committee members in the course of their deliberation have weighed the best available evidence and have taken input from the public, which has also been considered. The public has also had an opportunity to comment on draft versions of the report and we have, in this document, a listing of the outcomes that we have considered in making the decision, and these have been prepopulated by staff. Are there other outcomes that we considered that aren't already on here that we should mention as factors that influence our decision making? I think we did consider some special populations, which are not listed here, including various clinical conditions that would put the patient at risk of low bone density, as well as medications, or medications on here. OK. We also considered the existing coverage decisions for Medicare, and we had a list of some other payers that were included in our decision making. We also looked to guidelines, which were also considered in our process, and that moves us to the first nonbonding voting question, and...

Christopher Shurhart: May I ask a clarifying question, please? Some of the guidelines point out the screening intervals, and you're differing with those and that's based on the Gourlay study in your analysis there.

Craig Blackmore: Yeah, I think we had a... we had a lengthy discussion and we felt that the evidence, particularly the Gourlay Study, but the best available evidence suggested that we could come up with repeat screening intervals that were more driven by the evidence than that which some of the other guidelines used, and that was the motivation for these... these values.

Christopher Shurhart: Thank you.

Craig Blackmore: OK. So, the first non... nonbinding voting question is whether we believe there is sufficient evidence under some or all situations that the technology is effective, safe, and cost effective, and so the... the construct here is that we would say for effectiveness, do we believe that under some or all situations using DEXA will basically improve the care of individuals who either have or are at risk for developing osteoporosis, and yeah. So, you can say that it is of unproven equivalent, less, or more effective.

Josh Morse: Ten more effective.

- Craig Blackmore: And then safety of the technology itself. So, is using this technology safer than not using it, less safe, equivalent, or unproven?
- Josh Morse: I see five equivalent, six equivalent, and that would be four unproven.
- Craig Blackmore: OK, and then cost-effectiveness of using the technology versus not using the technology?
- Josh Morse: Nine unproven, one more.
- Craig Blackmore: OK, do the committee members want any further discussion based on where we are or else I will move to the final vote? OK. So, we'll move to the final vote and the committee members have three choices. They can choose to not cover the DEXA under any circumstances. They can choose to cover DEXA unconditionally whenever it is requested, or they can choose to cover it under certain conditions, and we have, through this process, predefined what those conditions would look like and they are on the board and so we'll vote.
- Josh Morse: Ten cover with conditions.
- Craig Blackmore: And then I think again the decision is similar to Medicare and some of the expert guidelines, though we did make some exceptions, particularly as we discussed previously about our repeat screening interval. We recognized absence of evidence in certain areas, such as the use of it immediately following fragility fracture and lack of evidence, for example, in many subpopulations of men and that evidence guided the areas where we did differ somewhat from some of the other guidelines and coverage decisions that are out there. Anything I left out on the process?
- Josh Morse: Nope. I think that... that's complete.
- Craig Blackmore: That completes DEXA scanning and osteoporosis screening, and I believe we're done. No, we're not done.
- Josh Morse: We do have another...
- Craig Blackmore: We are not finished.
- Josh Morse: ...agenda item.
- Craig Blackmore: This item is finished, but we do have another agenda item, and why don't we grab our lunches, which are boxed lunches, and then we will sit here and we will have an opportunity to preview some upcoming topics and have input into the key questions. That's where we are, right, questions... or?
- Josh Morse: There's no input on key questions today, but we'll update you on where we are with that.
- Craig Blackmore: So, we'll get an update.

Josh Morse: On other projects.

Craig Blackmore: Very good. So, grab your lunches. We are still in session.

We're still in session. So Josh is going to update us.

Josh Morse: So, this is a new... we're just going to provide an update on what's going on, since we've changed the schedule and... of the meetings. You'll note that we have between now, which is November, and May we'll do all of the topic reviews, as we did last year when we... we changed this. So, we're going to give you a preview. We don't have any open scope or... or key questions today to present to you. We may at the January meeting. We are currently working on the early development of the... the tympanostomy tubes project there at the bottom. So, we may have draft key questions for that project at the January meeting, but I'll just quickly give you an update on where we are with each of these. So, the neuroimaging for dementia topic, there is a draft final report. I believe the... the comment period on that closed yesterday. So, that was the last day of comment on the... the draft report. We will have that meeting on January 16th. Also that day, there is the appropriate imaging for breast cancer topic and the comment period actually for that is open today through the end of the day basically. So, if you were interested in looking at that report and providing comment, there is the rest of the day for comment on that.

The testosterone testing topic is in the draft report phase right now. I don't believe that that's been published, but I have details on each one of these, so we'll go through this individually. So, again, the context for the neuroimaging topic is here on this slide. There are... I'll just read it. There are significant questions related to the use of functional neuroimaging for the diagnosis of primary neurodegenerative dementia and mild cognitive impairment, and again, we'll bring that to the meeting on January 16th, and here, again, is the schedule for that. Like I said, the comment period just closed yesterday, and that's all the information on that. So, the... the point of this update. We talked about this in September at the retreat was just to give you a heads up on, on where we are. So, if you have questions about the process, I guess now is, now is the right time on any of these. So, just interrupt me if you have any, have any questions for me or for the agencies that selected these topics.

So, the appropriate breast imaging, or imaging for breast cancer screening in special populations, here's the policy context. I will read this. So, the... to assess the potential for digital breast homosynthesis, to replace digital mammography as a frontline screening tool in asymptomatic women, and to assess the use of supplemental screening among women with a normal mammogram that is with no abnormalities detected but with dense breast tissue that might obscure an abnormality. So, those are the questions that are being addressed in that report.

Kevin Walsh: So, is the second one the use of... where it says supplemental screening, an EEG?

Craig Blackmore: It's usually ultrasound or maybe MR.

- Kevin Walsh: Right, I know what the standard is now, but I didn't understand that wording.
- Josh Morse: There is more detail on the website here if you... we just have the high level on the slides.
- Richard Phillips: [inaudible].
- Chris Standaert: [inaudible] a couple years ago, I thought.
- Josh Morse: Right, and it's... I don't... it doesn't completely overlap. Dr. Blackmore will answer that question.
- Craig Blackmore: So, there's... there's an understanding that breast density is a... is a predictor of development of breast cancer, basically. It's a risk factor on some level, and so there are... there is now legislation in a number of states around the country, and considering this, and being considered, in my understanding is, I don't know, but in this state to require with a mammogram report that you tell the woman the density of her breasts, and if she is in a higher density cohort in some, you know, that's the question, but some people believe in a higher density cohort because they may be at a slightly higher risk that you should offer additional screening to go with the mammogram. It might be an ultrasound. It might be an MRI scan, and that's the context. So, it's not... what we looked at before was high-risk women. So, it was women who had family history or something that put them in a really high-risk group. This is a different topic. It's... it's women whose basically normal but on the mammogram their breasts... they have dense breasts and that puts them at a slightly increased risk, so should we do something differently?
- Man: And do you know, I'm sure you know the literature about this.
- Craig Blackmore: I am somewhat familiar with the literature.
- Man: Does it distinguish between types of breast cancer?
- Craig Blackmore: I... I don't know the answer to that actually, and that, I mean, that's the framework. Obviously, we'll discuss the topic when we discuss the topic, but just so you understand the difference between this and what we looked at before, which was MR in women with, you know, family history or [inaudible] or whatever.
- Man: I'm just... the implication of high... high density... of highly-dense breasts being associated with cancer is in my mind a little general.
- Craig Blackmore: Well, we'll need to look at the evidence. I'm just... I'm... I'm telling you what the belief is, and we can drill down on it, but that's sort of the setting.
- Josh Morse: And that, again, is open through the end of the day as far as looking at that draft report if you have any questions about the evidence that's in or not in... in there.

So, beyond January, we are working on the testosterone testing topic and the context is here on the screen. There's controversy and uncertainty concerning the criteria, diagnostic criteria for hypogonadism, techniques for measuring the testosterone levels, cutoff values for normal, benefits and harms of treatment, and optimal intervals for repeat testing, and looking here... so the draft report will be published in a couple weeks. It's not out yet, and of course there'll be a comment period that goes for 30 days and the meeting is scheduled for March.

Marie Brown: Excuse me, did that cover the... the rationale for screening in the first place? Is it screen, I mean... the rationale for ordering the tests?

Josh Morse: Did Teri... Teri is actually writing this report now. We don't have the key questions here. I believe the re-... the report will cover that, at least in the background, what is the circumstance where testing might be indicated.

Marie Brown: That's the key.

Seth Schwartz: I want to ask Dr. Hammond if he wants to comment on that.

Steve Hammond: I thought that was the crux of the issue is when is it appropriate to test testosterone levels? So, what you've got listed there is policy context. That's, I think... those are some of the reasons why we want to look at testosterone testing and when it's appropriate, when it's indicated, when it...

Chris Standaert: [inaudible]

Steve Hammond: Well, both... but it... it rises out of the concern that treatment is being promoted for mild abnormalities of testosterone levels, mildly low testosterone.

Chris Standaert: So, part of the question would be when should you treat? Is that...

Steve Hammond: Well, I... yeah...

Chris Standaert: ...what kind of...

Steve Hammond: ...I would like to see the key questions, but as I recall, it's really about when is it appropriate to test in the first place?

Josh Morse: This report will only look at testing. It won't look at treatment.

Woman: [inaudible]

Josh Morse: Yeah, the key questions, I can access them there.

Richard Phillips: Is this adult population only?

Josh Morse: Good question.

Steve Hammond: I believe it's... it's targeted at adults. That was the intention... and I'd love to see the PICO... or there we go. Can you go up and look at the PICO, yeah, adult men?

Marie Brown: Can you scroll down to the key questions?

Josh Morse: So, any other thoughts on this?

Chris Standaert: I don't know. I just... I guess I could see a similar problem [inaudible] data. The real concern is the use of testosterone to treat hypogonadism, and there's a... this is a surrogate way of getting about it, just looking at what triggered this test and not so much when should you really be treating somebody, and the harms for the test aren't the tests. The harms are what happened because of the test, but we're not looking at treatment, and we may not get a lot about what happens because of the test, you know, if the problem's the treatment, we're looking at the testing not the treatment.

Steve Hammond: Right, I mean...

Chris Standaert: So, we may wind up saying something, but we may not really be giving it the issue we're after, which is when should you treat, are the reasons not to treat, are there also benefits to treatment in... in specific risk factors you're treating or not treating from the testosterone and that's a different question than when do you test... and frankly if the test is the limiting factor and it's basically you can't test unless the test is \$20, people get the test and [inaudible].

Steve Hammond: Right.

Chris Standaert: So, I... I don't... I just want to make sure that this gets at what you want it...

Steve Hammond: Right.

Chris Standaert: ...if your concern is how often testing is being done, we might get at that. If your concern is the impact once you have the test, this will be hard... this is a tangential way of doing it, and I can see that.

David McCulloch: Well, I think we've thought this was part of the... the potential problem, or overtreatment with questionable benefit and I mean...

David McCulloch: I... I... think that is the big issue Steve. I mean, there is massive advertising for anybody who watches or listens to any sport program there are several companies who claim if you're a guy over the age of 40, we all slow down. It could be a treatable cause. You should now have your testosterone, and for many of us, it'll be way down in... in the low end of the normal range. You should come and see us, and we'll treat. I mean there is a massive marketing campaign to over diagnose and say and... and treat it to dangerously high... or whatever, and I'm quite sure there'll be a lot of people in the public comment period coming, you know, promoting that, because it's been promoted as, you... you can feel 25 again.

- Chris Standaert: Do you think we'll get it with this [inaudible].
- David McCulloch: Well, that... that... I agree with you. I... I wonder if...
- Steve Hammond: Well, it... it is a little bit oblique, but my understanding is that the Health Technology Assessment is not really scoped to look at drug utilization.
- Chris Standaert: True.
- Steve Hammond: And so we... but we thought part of the problem is excessive screening.
- Josh Morse: It's very similar to the vitamin D topic.
- David McCulloch: It... it is.
- Josh Morse: Yeah.
- David McCulloch: And, and maybe if we can just... this might get at it from your point of view. We can clarify under what circumstances do... do you do it... and...
- Josh Morse: Right, and we do see trends in the testing.
- David McCulloch: Yeah. I'll bet you do.
- Richard Phillips: But I...
- Seth Schwartz: I... I think that's legitimate, but I still think for us to answer the question, it would be useful to know what the efficacy data is about treatment. So, I mean... I mean... because that's kind of where we were today where we... peripherally there was some not... there was some stuff and there was some knowledge because of our clinical expert, but we were really dependent on the clinical expert to say yeah, this stuff works, but we don't really know. We didn't really look at that. It would be sensible to at least look at that data. Maybe that should be a better key question. Even if it's not going to, you know, affect what the policy is regarding testing, it could help us to make the decision.
- Chris Standaert: If, yeah... if you knew treatment didn't really alter long-term outcomes, then you'd say testing is...
- Kevin Walsh: But it's even worse than that. Treatment might increase risk.
- Craig Blackmore: Absolutely.
- Kevin Walsh: And I think that... I... I think you could potentially get at this with the second part of number two, but I think we have to... I think what we're all saying is... even though we're not being asked to render a decision on the use of testosterone, in order to evaluate the potential harm of testing you need to know what follows it... and you need... you need to know the evidence.
- Steve Hammond: That should be in the background.

- Josh Morse: Right. So, it'll be more than in the background. I believe, in my understanding of how the literature's being searched... there will be... they are looking for the indirect evidence, as far as the outcomes, because there will be no direct evidence that, you know, nobody has studied, you know, what happens to a person who gets attached and ultimately what is their...? Is there an improvement in their health outcome? But there is the... the more indirect or intermediate steps where you can look at the treatment information for some conditions and find out if that in fact can help outcomes, and that's what's happened, but that...
- Seth Schwartz: Is that... that is in there?
- Josh Morse: Yes.
- Seth Schwartz: That data will be presented to us?
- Josh Morse: Yes. That's being dredged as part of the report, but the report will be available on December 15th or before and, you know, I would encourage you to look at it if you have these questions when it comes out.
- Marie Brown: So, we would see placebo controlled trials then of the use of testosterone?
- Josh Morse: No.
- Chris Standaert: I can see you coming out with studies that look at testosterone test and treatment because they don't mention testing and then [inaudible] talking about harms, and so they don't, they fall out and then we're... they're going to have studies on does this... does this work or does this help in some way or not and we're not going to get them because we're not asking for them, so... and then we're going to sit here and go... well we'd like to know that.
- Marie Brown: I mean... but if we knew that... that the RCT said that there was no difference, that would help if you found that there was no indication for screening, that would strengthen that argument.
- Chris Standaert: Right. It's sort of like we had today with... we had the... the test and the treatment are sort of lumped together in what we did today, and it made it difficult to really pull out the test [inaudible].
- Craig Blackmore: Yeah, I think to know that the test has value, we would have to know that there was an effective treatment and that that treatment had differential effectiveness based on the value of testosterone, and so there's two pieces to that. The test has to be good at determining what the value is, and that determination has to feed into a differential effectiveness, a different threshold. So, in order to get at that, we need to make sure we get all of the information on every trial that's ever been done of testosterone so we can understand what the criteria were for entry into that trial and we can understand how a test might help improve that outcome. I'm giving you a window to make sure that all of that information...

Josh Morse: Understood.

Craig Blackmore: ...is included under...

Josh Morse: Yes.

Craig Blackmore: ...this topic.

Josh Morse: Yes. We... we have had the conversation about it... at least seeking the reviews that have looked at the effectiveness of testosterone treatment to understand what the entry level criteria were for the studies that are there.

Craig Blackmore: We need to know the entry level criteria and the effectiveness.

Josh Morse: Right.

Craig Blackmore: And the strength of evidence of effectiveness at each different...

Marie Brown: Yeah, especially RCTs.

Craig Blackmore: And criteria threshold.

Chris Standaert: [inaudible] and they'll get at that. We've been down this road.

Josh Morse: Right. So, there's...

Chris Standaert: [inaudible] that topic.

Josh Morse: Okay. So, we'll have this report in a couple weeks, and we'll make sure that it's available...

Chris Standaert: We tried to warn you what we'll say.

Josh Morse: ...for review, yeah.

Chris Standaert: That's why we're here, right?

Josh Morse: That's why we're here. OK, and we just finalized the key questions for this topic, imaging for rhinosinusitis. Here's the policy context. So, the radiological imaging for evaluation of chronic sinusitis represents an area of substantial utilization in plans managed by Washington. Since imaging is insufficiently accurate to service the gold standard for the diagnosis of rhinosinusitis, an understanding of its appropriate role is important. We're developing an evidence-based assessment of the accuracy of different imaging modalities for confirming or refining diagnoses of rhinosinusitis and the impact on outcomes and the cost warranted to guide coverage policy. So, this is scheduled for review at the May meeting along with bariatric surgery and, as I said, we just finished the key question document as a final document. The draft report is due in February.

- Kevin Walsh: Who's the clinical expert? Did we appoint anyone yet?
- Josh Morse: We have not identified, actually... I... I should say, no, there is a tentative clinical expert.
- Kevin Walsh: Who is that?
- Josh Morse: Doctor... I believe her first name is Amy Anstad, in Seattle. I spoke with Dr. Anstad and I have... I have an agreement I believe that she... and I will have to follow up with her.
- Chris Standaert: And the nonimaging based methods of diagnosing rhinosinusitis would be considered an addition to [inaudible] or is this purely [inaudible].
- Kevin Walsh: It's just clinical.
- Chris Standaert: But, so are they going to look for things comparing the clinical diagnosis of sinusitis to the equal amount of benefit added by...
- Craig Blackmore: Do we have the key questions?
- Josh Morse: Margaret, can you pull the key questions up for this?
- Richard Phillips: Is the bariatric surgery going to include kids, too?
- Josh Morse: We'll... we'll get to that one next.
- Marie Brown: I know some clinics are going to be here in the mass.
- Craig Blackmore: So, the challenge here is what you mean by accuracy. It's very, very good at saying something is wrong, but it's... the challenge is identifying chronic versus acute, bacterial versus nonbacterial, and so what do we mean by accuracy? Are these final or are we in the...
- Josh Morse: These questions...
- Craig Blackmore: ...where are we?
- Josh Morse: ...are final.
- Craig Blackmore: OK.
- Josh Morse: But if you have guidance...
- Craig Blackmore: So, as we... as we... as we structure the literature review around these questions, let's make sure we're explicit on what we mean by accuracy, which gets... your second question gets into it... is the... is the clinical management decision, because I mean, that's really what you want to do. You... you can find

all sorts of stuff on a sinus CT, but it has to be able to guide management that leads to better outcome.

Chris Standaert: And then you have questions of your gold standard.

Craig Blackmore: There is no gold standard.

Chris Standaert: I know, but, you get the accuracy, that's what... you're going to have to... you'll have to compare everything of some sort and I guess that very question of imaging versus clinical diagnosis does have incremental, you know, benefit... I mean...

Richard Phillips: Right, is there a clinical comparator?

Chris Standaert: Yeah [inaudible].

Richard Phillips: Because that's... that's really what we're... what we're comparing it to. That's what you're saying, clinical diagnosis.

Chris Standaert: Mm-hmm, that will be this clinical comparator I would think.

Craig Blackmore; I mean, the other piece of this is that it... you can use sinusitis on somebody the day they get sick. You can use sinusitis, sorry, you can use sinus CT on somebody two weeks later, or you can use sinus CT on somebody who's been treated for three months with multiple courses of antibiotics, and, you know, there... there's just... those... those different contexts are going to give you completely different results.

Seth Schwartz: Right, and you want to... and we want to, you know, it'd be nice to have information on all three of those contexts.

Craig Blackmore: Yes.

Richard Phillips: The other thing is that there is the hospital comparator, one of the things they use there is the simultaneous use of sinus imaging with other standard head and neck...

Craig Blackmore: It's simultaneous... a head CT and a sinus CT performed in the same day they use as a marker for...

Richard Phillips: Right, and I think that...

Craig Blackmore: ...over-utilization.

Richard Phillips: ...that the normal across country is somewhere around 10%.

Craig Blackmore: And, and you can...

Richard Phillips: You know that... of... I mean... that's what the mean... the median is, and it doesn't mean that's what the right answer is, but I guess what I'm really getting

at is there... within the framework of how this thing is going to be looked at, that's important data to be brought into the... to the discussion, I would think.

Craig Blackmore: That's... yeah.

Richard Phillips: Because that's... that's defined by NQF, you know?

Josh Morse: Can you scroll back up? So, I just wanted to point out that in the population, which is a little bit higher, we are trying to get at the question of chronic acute or recurrent.

Marie Brown: All three?

Josh Morse: So, we'll be seeking the evidence if it's identifiable that way.

Craig Blackmore: OK. OK, well... I mean... I think you've got... your second bullet point covers what's important, and... and that is how it affects management and how that secondarily relates to outcome. The... the accuracy piece is more... less clinically relevant. I don't know. Seth, do you get [inaudible]?

Seth Schwartz: Well, I mean, it... the only context is if you're looking at, if you're... looking at a comparison of those different studies. So, you know, I mean... CT is going to be more accurate than ultrasound and x-ray is going to be... So, the [inaudible]... but I think the ultimate question of interest is, should you be ordering any imaging studies for patients with acute sinusitis? I mean, there's guidelines that say no, which are [inaudible]. So, I think we'll ultimately come to that conclusion, but I think it's... I don't think it's an unreasonable, you know, I... I don't think it's an unreasonable way... way of looking at the question.

Craig Blackmore: Yeah, and... and the reason you can come to that conclusion is not because of the accuracy of the study. The accuracy is actually pretty good. It's that it doesn't matter.

Chris Standaert: Right.

Richard Phillips: Yeah.

Craig Blackmore: If it doesn't predict how... if it doesn't tell how you should treat in an acute setting.

Seth Schwartz: But I will say that that's in the acute setting. So, there... it's slightly different when you look at the chronic setting. So, I... so there's different situations, and you're answering different questions.

Craig Blackmore: Yeah.

Seth Schwartz: Is this patient a surgical candidate or other things? As oppose... and then... so then the accuracy is important because if they have a normal sinus CT but they've had clinical symptoms of sinusitis for three months, you're still not going to operate on that patient.

- Craig Blackmore: Mm-hmm.
- Seth Schwartz: So there's, you know, they're... they're different clinical scenarios.
- Craig Blackmore: So, the chronic, acute, and recurrent is also very important. So, it's there... hopefully they [inaudible].
- Josh Morse: So, we will bring you the evidence for that and again, that one's due in February, the report... draft report. OK, so the last topic for this year will happen again in May, and that's bariatric surgery. This will update the original pediatric bariatric surgery, and it will move beyond just pediatrics to include anybody who might be eligible for bariatric surgery. So, here's the policy context, weight loss, success rates from lifestyle modifications alone have been modest, at best, and the risk-benefit tradeoffs for weight loss medications are in question. Uncertainties exist regarding the relative performance of each type of procedure and specific patient populations. For example, adults versus pediatric patients, moderately versus severely or moderately obese, etc. There are conflicting data on the long term benefits. So, this report is in process.
- David McCulloch: Have you identified an expert?
- Josh Morse: We've had two individuals step forward and offer to be experts, yes.
- David McCulloch: You... you don't have their names off hand?
- Josh Morse: Dr. Sun from Swedish, I believe is one, Brian Sun, and there's a Dr. Michaels, I think, also from Swedish.
- David McCulloch: Hmm. I can suggest two others.
- Josh Morse: OK, I will follow up with you. If they are not... if we... if this doesn't work out with the two that have come forward.
- Marie Brown: Do we want to put body mass index instead of obesity or not, I mean, a certain...
- Josh Morse: Margaret, can you call up the... the key question document on this is extensive, and we have very detailed questions here, so.
- David McCulloch: That... that will come out. I mean... all... all the discussions are... are... on what BMI cutoffs with or without chronic conditions like diabetes, I mean, I deal with this stuff all the time. So, the... the question of BMI will come up.
- Marie Brown: Yes. I mean, that's been really key in the evidence about how these people, what BMI they use.
- Chris Standaert: So, that's sort of what [inaudible] as opposed to what, you know, predictive factors about the patient, patient-specific factors that predict outcome.

- Josh Morse: So, that's a separate question if you can scroll down, Margaret.
- Chris Standaert: I don't see that one. Oh, there's more questions.
- Josh Morse: Yeah, there's more questions.
- Chris Standaert: OK.
- Josh Morse: So, I think we tried to get at that two different ways.
- Richard Phillips: I can't remember, but it seems to me that the... when we did this study before, that kids over the age of 18, between 18 and 21 were put in... grouped in with adult by some of the studies. Did you look at that?
- Josh Morse: So, we are sensitive to that question and key question one is very... tries to be very clear about how it's going to break out the age groups.
- Richard Phillips: OK.
- Josh Morse: There is... I think there's a sixth question.
- Richard Phillips: More often than not, those patients are operated on by non-pediatric surgeons, you know.
- David McCulloch: We presumably are going to look at comparing the different types, you know, band versus roux-en-Y versus vertical sleep, gastrectomy.
- Josh Morse: Right. So, all of those should be an all-inclusive report as far as range, comorbidities, surgical type.
- Man: [inaudible].
- Josh Morse: Unfortunately, that is not the case right now. The rhinosinusitis topic is scheduled for the same day in May. So, hopefully it'll be enough time that day. So, can we switch back to the other one, Margaret? Thanks, very much. So, this meeting will be followed up by... we are again, planning a July meeting. I'm not sure... is that July meeting scheduled now for...
- Christine Masters: July 10th.
- Josh Morse: July 10th, Friday. We, we are planning to do the same thing we did this year with a... a teleconference to work this out. So, scheduling beyond July, we are currently working on this topic, tympanostomy tubes and I will again quickly go through the policy context. So, there are significant questions related to use of tympanostomy tubes for the treatment of otitis media with effusion in children under 16. These include safety, efficacy, differential efficacy and safety in subgroups and costs. So, we don't have draft key questions on this, so I am hopeful, given the... I think these are really valuable conversations we have with you and, you know, we're trying to schedule such that key questions drafts overlap with these meetings. So, I think this will be ready by July, or January

16th, anyway, for your next meeting, and we'll try to find some time in that agenda to show you how we... what we've developed for key questions there, but this is currently scheduled for a year from now for public meetings, so that's how far out we're looking right now. We'll have other topics that we'll have key questions. I'm not anticipating another set of key questions for January but perhaps for March. Likely for March we'll have at least one if not more for the... the next seasons, so...

Marie Brown: This is helpful, Josh.

Richard Phillips: Yeah.

Marie Brown: It really is.

Josh Morse: Good. We may have a clinical expert for this. I'm not sure. So, I'll follow up with the... the group that's writing this to find out. So, that is all I have on this. Craig, do you want to adjourn the meeting, or...?

Craig Blackmore: The meeting is now adjourned. Thank you all.

Josh Morse: Thanks very much. Take care.